

Pediatric moyamoya disease presenting with intracerebral hemorrhage

- Report of three cases and review of the literature -

Kazuhiko Suyama, MD^{a,*}, Koichi Yoshida, MD^b, Hideaki Takahata, MD^b, Keisuke Toda, MD^b, Hiroshi Baba, MD^b, Yasunari Ishikawa, MD^c, Makoto Hirose, MD^a, Izumi Nagata, MD^a

^a Department of Neurosurgery, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki 852-8501, Japan

^b Department of Neurosurgery, Nagasaki Medical Center, Omura, Nagasaki 856-8562, Japan

^c Department of Neurosurgery, Okinawa Chubu Hospital, Uruma, Okinawa 904-2293, Japan

Abstract

Intracerebral hemorrhage in patients with moyamoya disease is rare in children. We report three unique cases of pediatric moyamoya disease with hemorrhagic onset. Two 7-year-old girls and a 9-year-old girl were admitted to our hospital because of intracerebral hemorrhage associated with angiographically verified moyamoya disease. Two of them did not demonstrate either an ischemic episode or cerebral infarct on the magnetic resonance images. A decreased regional cerebral blood flow was revealed on single photon emission computed tomography in two patients, who developed cerebral infarction in the acute stage following hemorrhage. They underwent superficial temporal artery-middle cerebral artery anastomoses combined with encephalo-myosynangiosis, and have not experienced any further ischemic episodes thereafter. Hemodynamic insufficiency associated with moyamoya disease could cause intracerebral hemorrhage even in children. Adequate management in the acute stage of hemorrhage and revascularization surgery are recommended to prevent

cerebral infarction, which may easily occur in pediatric patients with moyamoya disease.

Key words: moyamoya disease, pediatric patients, intracerebral hemorrhage, cerebral infarction, edaravone

Headings: Hemorrhagic moyamoya disease in children

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; SPECT, single photon emission computed tomography; IMP, N-isopropyl-4 iodoamphetamine; CBF, cerebral blood flow.

Correspondence: Kazuhiko Suyama, MD, Department of Neurosurgery, Nagasaki University Graduate School of Biomedical Sciences, 1-7-1 Sakamoto, Nagasaki 852-8501, Japan
E-mail: ksuyama@nagasaki-u.ac.jp

1. Introduction

Moyamoya disease is characterized by the progressive occlusion of the internal carotid arteries with spontaneous development of a collateral vascular network [1]. Pediatric patients mainly present with cerebral ischemia and they very rarely bleed [2, 4, 14, 15]. Although the benefits of surgical revascularization for ischemic moyamoya disease have been well recognized, the indications for such treatment in hemorrhagic type to prevent rebleeding have not yet been established [2, 6, 13, 20, 22, 27]. We herein report three children aged < 10 years presenting with intracerebral hemorrhage associated with moyamoya disease, two of which were accompanied with early ischemic complications followed by revascularization surgery.

2. Case report

Patient 1

A previously healthy 7-year-old girl suddenly suffered severe headache and vomiting on November 17, 2004. She developed moderate weakness in her right extremities, and was admitted to our hospital by ambulance. Computed tomography (CT) demonstrated an intracerebral hemorrhage in the left globus pallidus and no cerebral infarction was evident on magnetic resonance image (MRI) (Fig. 1). Cerebral angiography revealed angiographic moyamoya disease (right side, Stage 2; left side, Stage 3 according to the angiographic criteria described by Suzuki [24]) without any cerebral aneurysms. Both vascular blush in the lenticulostriate arteries and dilatation of the anterior choroidal artery were prominent in the left side. Single photon emission computed tomography (SPECT) using ^{99m}Tc -ethyl cysteinate dimer (ECD) obtained on the 9th hospital day showed a modest, and not significant, reduction in the regional cerebral blood flow (CBF) in the left frontoparietal cortex. The cerebral vascular reactivity to acetazolamide remained normal. She was managed conservatively with hydration and her hemiparesis gradually improved. She has not experienced any further neurological episodes and she is not on medication during the 28- month follow-up after the first ictus.

Case 2

A previously healthy 7-year-old girl experienced severe headache and vomiting on June 9, 2005. She was taken to a local hospital, and then transferred to ours because of her decreased level of consciousness. CT on admission demonstrated an intracerebral hemorrhage in the right paraventricular white matter and intraventricular clots, but no evidence of cerebral infarction was observed on MRI (Fig. 2(A)(B)). Cerebral angiography revealed angiographic moyamoya disease (right side, Stage 3; left side, Stage 1) without aneurysmal formation. Both vascular blush in the lenticulostriate arteries and dilatation of the anterior choroidal artery were prominent on the right side. SPECT using N-isopropyl-4 iodoamphetamine

(^{123}I -IMP) obtained on the 4th hospital day showed a marked reduction of regional CBF in the right parietal cortex (Fig. 2(C)). She was treated with the intravenous administration of a hyperosmotic agent (400 ml/day glycerol, 10 w/v% concentrated glycerin solution). Thereafter, she became alert and her headache subsided.

On the 16th hospital day, she complained of a severe headache and began to cry. Soon thereafter, she demonstrated mild left hemiparesis. MRI revealed multiple infarcts in the right frontal and bilateral parietal subcortexes (Fig. 2(D)(E)). A free radical scavenger, edaravone [25], was intravenously administered (60 mg/day) for 5 days, and her left hemiparesis gradually improved. She underwent a superficial temporal artery-middle cerebral artery (STA-MCA) anastomosis combined with encephalo-myo-synangiosis (EMS) on the right side on the 47th day after the last ictus. She has not experienced further ischaemic episodes without any medication during a 20- month follow-up after surgery. Postoperative cerebral angiography showed a good patency of the direct bypass, and an increased regional CBF in the right cerebral hemisphere was evident on SPECT using ^{123}I -IMP.

Case 3

A 9-year-old girl suddenly experienced a severe headache and became lethargic on October 29, 2005. She was taken to a local hospital, and then was referred to our institution. She had a previous history of occasional headaches since 3 years of age and transient weakness of the right upper extremity at 8 years old. CT revealed a tiny intracerebral hemorrhage in the right paraventricular white matter and clots in the right lateral ventricle (Fig. 3(A)). MRI on admission did not show any other ischemic lesions (Fig. 3(B)). Cerebral angiography revealed angiographic moyamoya disease (right side, Stage 2; left side, Stage 3) without aneurysmal formation. The dilatation of the left anterior choroidal artery was prominent, while neither the anterior choroidal artery nor the posterior communicating artery showed abnormal dilatation and branching in the right side. SPECT using

^{123}I -IMP obtained on the 6th hospital day showed a modest, and significant, reduction of regional CBF in the left frontoparietal cortexes (Fig. 3(C)), which was on the opposite side to the bleeding. She was treated with the intravenous administration of a hyperosmotic agent (400 ml/day glycerol, 10 w/v% concentrated glycerin solution). She became alert and her headache subsided.

On the 7th hospital day, she had a recurrence of the headache and manifested transient right hemiparesis several times. Diffusion-weighted MRI revealed an infarct in the left frontal subcortex (Fig. 3(D)). Ederavone [26] was intravenously administered (30 mg/day) for 5 days, and her ischemic attacks did not progress to a complete stroke. She underwent STA-MCA anastomosis with EMS on the left side on the 40th day after the last ictus. She has not experienced any further ischemic episodes without medication during a 15- month follow-up after surgery. Postoperative cerebral angiography showed a good patency of the direct bypass, and an increased regional CBF in the left cerebral hemisphere was evident on SPECT using ^{123}I -IMP.

3. Discussion

Hemorrhagic type moyamoya disease is frequently seen in adults [1], and quite a low incidence of hemorrhage in patients aged < 16 years has been reported both in Japan [2, 15] and Korea [4, 14]. In adults, rebleeding is not uncommon and it could worsen the prognosis following hemorrhage [7, 27]. In contrast, the natural course following the first hemorrhage in children remains unclear because of the limited number of reports regarding this kind of episode. Morioka et al. [17] reported a long-term observation following hemorrhage in two children who had not undergone revascularization surgery, and one of whom experienced recurrent hemorrhage in patient's 30s. In contrast, others have reported neither recurrent haemorrhage nor any ischaemic events following hemorrhage among children who had undergone surgery, despite the absence of either

long-term observations or precise descriptions [8, 10, 12, 27].

The increased bleeding risk in adults is considered to result from the fragility of the basal moyamoya vessels and the medullary arteries derived from the choroidal arteries, both of which have developed as long-term compensation for decreased regional CBF [8]. However, in our cases, only one had a previous ischemic episode and none had ischemic lesions demonstrated on the initial MRI. In terms of the bleeding hemisphere, the predominant angiographic findings in adults have been reported as disease progression to Stage 3 according to Suzuki's angiographic criteria [15, 24]. In our case 3, bleeding appeared in the hemisphere where the angiographic staging was less advanced and the regional CBF remained normal (Table). It was also noted that both the anterior choroidal artery and the posterior communicating artery did not show the type of abnormal dilatation and branching that have been reported to be predominant in young patients with hemorrhage as well as adults [18]. These findings suggest that hypoperfusion is not necessarily responsible for bleeding, and that non-chronically hemodynamic stress may cause intracerebral bleeding from the especially vulnerable collateral vessels, even in children with moyamoya disease.

Subsequent ischemic complications can be a major concern in the acute phase of bleeding in patients with moyamoya disease. Suspected hemodynamic insufficiency and an increased intracranial pressure following hemorrhage can induce cerebral ischemia. In addition, both hyperventilation following crying and dehydration following the use of hyperosmotic agents may thus play a critical role in the cerebral hemodynamic conditions right after bleeding in pediatric patients. In our cases 2 and 3, the ischemic events appeared within 16 days of the first ictus in the region where regional CBF had decreased (Table). We successfully used edaravone [26] to prevent further ischemic events instead of using antiplatelet agents that may have adversely affected the intracerebral haemorrhage. Iwama et al. [10] and Rafay et al. [21] reported similar cases to ours with ischemic complications. These findings raise the possibility

that subsequent ischemic complications may be easily induced in pediatric patients following intracerebral hemorrhage. Adequate sedation [19], hydration [10], and management against increased intracranial pressure [21] are crucial factors in the acute phase of bleeding in children with moyamoya disease.

The efficacy of revascularization surgery for ischemic moyamoya disease is generally recognized, while that for the hemorrhagic type in adult to prevent rebleeding has not yet been established [25]. Although some reports have demonstrated the effects of direct revascularization surgery to prevent recurrent bleeding [13], or at least subsequent ischemia [20], the long-term efficacy of revascularization surgery following hemorrhage in adult patients remains controversial [2, 6, 22, 27]. On the other hand, moyamoya disease in childhood manifests cerebral infarction more frequently than in adults. Because of the possible limitations regarding the oral intake of antiplatelet agents following intracranial bleeding, surgical revascularization for the region where regional CBF had decreased should be justified to prevent cerebral infarction in pediatric patients with hemorrhage. In our cases 2 and 3, in whom a subsequent infarction had developed, we performed direct revascularization combined with indirect procedures in order to obtain both a rapid improvement in CBF to prevent further ischaemic attacks [3, 9, 11, 16] and the long-term patency of the bypass [5]. They have not experienced any further ischemic episodes thereafter. Another concern is whether revascularization surgery performed in childhood for hemorrhagic moyamoya disease can reduce the rebleeding risk when patients reach the age range of 46 to 50 years, which is the age range with the highest likelihood of rebleeding [17]. Although the long-term effect of revascularization surgery on the prevention of hemorrhagic episodes in pediatric patients with ischemia has been reported [7, 8, 23], the follow-up findings of those with hemorrhage should thus be clarified by further long-term follow-up studies.

In conclusion, hemodynamic insufficiency could cause not only cerebral infarction but also intracerebral hemorrhage even in children with

moyamoya disease. The adequate management in the acute phase of bleeding and revascularization surgery is therefore recommended to prevent cerebral infarction which may easily occur in pediatric patients with hemorrhagic onset. Because the efficacy of revascularization surgery in preventing rebleeding remains unclear, further long-term follow-up studies are thus called for.

References

- [1] Fukui M. Current state of study on moyamoya disease in Japan. *Surg Neurol* 1997; 47: 138-43.
- [2] Fujii K, Ikezaki K, Irikura K, Miyasaka Y, Fukui M. The efficacy of bypass surgery for the patients with hemorrhagic moyamoya disease. *Clin Neurol Neurosurg* 1997; 99 (Suppl): 194-5.
- [3] Golby AJ, Marks MP, Thompson RC, Steinberg GK. Direct and combined revascularization in pediatric moyamoya disease. *Neurosurgery* 1999; 45: 50-60.
- [4] Han DH, Kwon OK, Byun BJ, Choi BY, Choi CW, Choi JU, Choi SG, Doh JO, Han JW, Jung S, Kang SD, Kim DJ, Kim HI, Kim HD, Kim MC, Kim SC, Kim SC, Kim SC, Kim Y, Kwun BD, Lee BG, Lim YJ, Moon JG, Park HS, Shin MS, Song JH, Suk JS, Yim MB. A Co-operative study: Clinical characteristics of 334 Korean patients with moyamoya disease treated at neurosurgical institutes (1976-1994). *Acta Neurochir (Wien)* 2000; 142: 1263-74.
- [5] Houkin K, Kuroda S, Ishikawa T, Abe H. Neovascularization (angiogenesis) after revascularization in moyamoya disease. Which technique is most useful for moyamoya disease? *Acta Neurochir (Wien)* 2000; 142: 269-76.
- [6] Houkin K, Kamiyama H, Abe H, Takahashi A, Kuroda S. Surgical therapy for adult moyamoya disease. Can surgical revascularization prevent the recurrence of intracerebral hemorrhage? *Stroke* 1996; 27: 1342-6.

- [7] Isono M, Ishii K, Kamida T, Inoue R, Fujiki M, Kobayashi H. Long-term outcomes of pediatric moyamoya disease treated by encephalo-duro-arterio-synangiosis. *Pediatr Neurosurg* 2002; 36: 14-21.
- [8] Irikura K, Miyasaka Y, Kurita A, Tanaka R, Yamada M, Kan S, Fujii K. The effect of encephalo-myosynangiosis on abnormal collateral vessels in childhood moyamoya disease. *Neurol Res* 2000; 22: 341-6.
- [9] Ishikawa T, Houkin K, Kamiyama H, Abe H. Effects of surgical revascularization on outcome of patients with pediatric moyamoya disease. *Stroke* 1997; 28: 1170-3.
- [10] Iwama T, Kotani Y, Yamakawa H, Nagata I, Hashimoto N, Sakai N. Cerebral ischemic complications following intracranial bleeding in patients with moyamoya disease. Three case reports. *Neurol Med Chir (Tokyo)* 2001; 41: 450-3.
- [11] Karasawa J, Toho H, Ohnishi H, Miyamoto S, Kikuchi H. Long-term follow-up study after extracranial-intracranial bypass surgery for anterior circulation ischemia in childhood moyamoya disease. *J Neurosurg* 1992; 77: 84-8.
- [12] Kawaguchi T, Hosoda K, Shibata Y, Kamei M, Kidoguchi K, Tamaki N. Usefulness and problem of multiple burr-hole operation for moyamoya disease. *Surg Cereb Stroke (Jpn)* 2000; 28: 81-90.
- [13] Kawaguchi S, Okuno S, Sakaki T. Effect of direct arterial bypass on the prevention of future stroke in patients with the hemorrhagic variety of moyamoya disease. *J Neurosurg* 2000; 93: 397-401.
- [14] Kim SK, Seol HJ, Cho BK, Hwang YS, Lee DS, Wang KC. Moyamoya disease among young patients; its aggressive clinical course and the role of active surgical treatment. *Neurosurgery* 2004; 54: 840-6.
- [15] Kobayashi E, Saeki N, Oishi H, Hirai S, Yamaura A. Long-term natural history of hemorrhagic moyamoya disease in 42 patients. *J Neurosurg* 2000; 93: 976-80.

- [16] Matsushima T, Inoue T, Suzuki SO, Fujii K, Fukui M, Hasuo K. Surgical treatment of moyamoya disease in pediatric patients. Comparison between the results of indirect and direct revascularization procedures. *Neurosurgery* 1992; 31: 401-5.
- [17] Morioka M, Hamada J, Todaka T, Yano S, Kai Y, Ushio Y. High-risk age for rebleeding in patients with hemorrhagic moyamoya disease: long-term follow-up study. *Neurosurgery* 2003; 52: 1049-55.
- [18] Morioka M, Hamada J, Kawano T, Todaka T, Yano S, Kai Y, Ushio Y. Angiographic dilatation and branch extension of the anterior choroidal and posterior communicating arteries are predictors of hemorrhage in adult moyamoya patients. *Stroke* 2003; 34: 90-5.
- [19] Nomura S, Kashiwagi S, Uetsuka S, Uchida T, Kubota H, Ito H. Perioperative management protocols for children with moyamoya disease. *Child's Nerv Syst* 2001; 17: 270-4.
- [20] Okada Y, Shima T, Nishida, M, Yamane K, Yamada T, Yamanaka C. Effectiveness of superficial temporal artery–middle cerebral anastomosis in adult moyamoya disease. *Cerebral hemodynamics and clinical course in ischemic and hemorrhagic varieties. Stroke* 1998; 29: 625-30.
- [21] Rafay MF, Smith SE, Dirks P, Armstrong D, deVeber GA. Hemorrhagic predisposing to cerebral infarction in children with moyamoya disease. *Pediatr Neurol* 2006; 34: 400-4.
- [22] Saeki N, Nakazaki S, Kubota M, Yamaura A, Hoshi S, Sunada S, Sunami K. Hemorrhagic type moyamoya disease. *Clin Neurol Neurosurg* 1997; 99 (Suppl): 196-201.
- [23] Suzuki SO, Matsushima T, Ikezaki K, Fujii K, Fukui M, Maeyama R, Nagatomi H, Kuromatsu C, Ito M, Matsunaga M, Matsuno H, Yamashita M, Matsubara T, Mannoji H, Kamikaseda K. *Surg Cereb Stroke (Jpn)* 1992; 20: 463-7.
- [24] Suzuki J, Kodama N. Moyamoya disease: A review. *Stroke* 1983; 14: 104-9.
- [25] The Japan Adult Moyamoya Trial Group. Study design for a

prospective randomized trial of extracranial-intracranial bypass surgery for adults with moyamoya disease and hemorrhagic onset. *Neurol Med Chir (Tokyo)* 2004; 44: 218-9.

- [26] Toyoda K, Fujii K, Kamouchi M, Nakane H, Arihiro S, Okada Y, Ibayashi S, Iida M. Free radical scavenger, edaravone, in stroke with internal carotid artery occlusion. *J Neurol Sci* 2004; 221: 11-7.
- [27] Yoshida Y, Yoshimoto T, Shirane R, Sakurai Y. Clinical course, surgical management, and long-term outcome of moyamoya patients with rebleeding after an episode of intracerebral hemorrhage. An extensive follow-up study. *Stroke* 1999; 30: 2272-6.

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; SPECT, single photon emission computed tomography; IMP, N-isopropyl-4 iodoamphetamine; CBF, cerebral blood flow.

Legends

Fig. 1

(A) A computed tomographic scan demonstrated an intracerebral hemorrhage in the left globus pallidus and intraventricular hemorrhage. (B) No cerebral infarction was evident on the T2-weighted magnetic resonance image.

Fig. 2

(A) A computed tomographic scan demonstrated an intracerebral hemorrhage in the right paraventricular white matter and intraventricular clots. (B) No cerebral infarction was evident on fluid attenuated inversion recovery (FLAIR) magnetic resonance image. (C) Single photon emission computed tomography (SPECT) using N-isopropyl-4 iodoamphetamine (^{123}I -IMP) showed a marked reduction in the regional cerebral blood flow in the right parietal cortex (arrow). (D) (E) FLAIR magnetic resonance images revealed multiple infarcts in the right frontal and bilateral parietal subcortexes.

Fig. 3

(A) A computed tomographic scan revealed a tiny intracerebral hemorrhage in the right paraventricular white matter (arrow) and clots in the right lateral ventricle. (B) FLAIR magnetic resonance images did not show any other hemorrhagic or ischemic lesions. (C) SPECT using ^{123}I -IMP showed a modest, and significant, reduction of the regional CBF in the left frontoparietal cortexes (arrow). (D) Magnetic resonance imaging showed restricted diffusion in the left frontal subcortex on the diffusion-weighted image.

Table

ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; Bil, bilateral; Angiographic Staging, staging according to Suzuki's criteria (Stroke 14: 104-109, 1983)

Fig. 1 (A)(B)

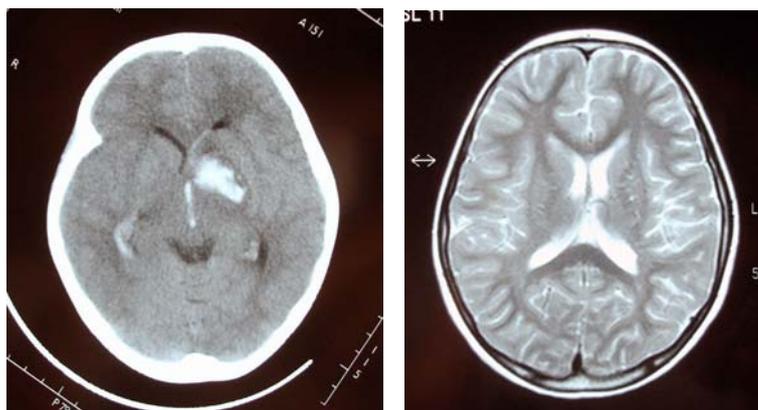
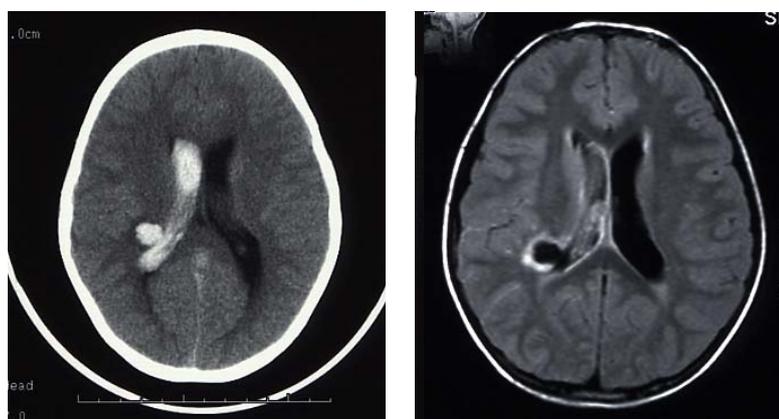
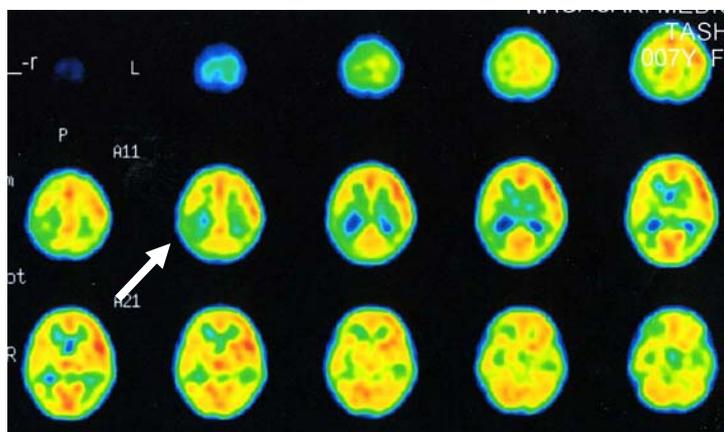


Fig. 2 (A)(B)



(C)



(D)(E)

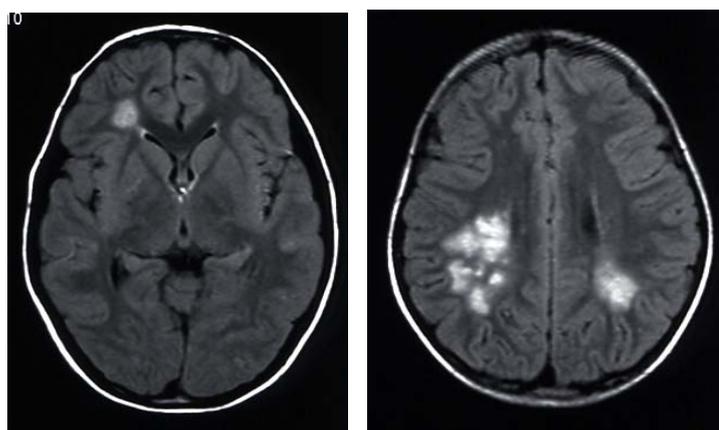
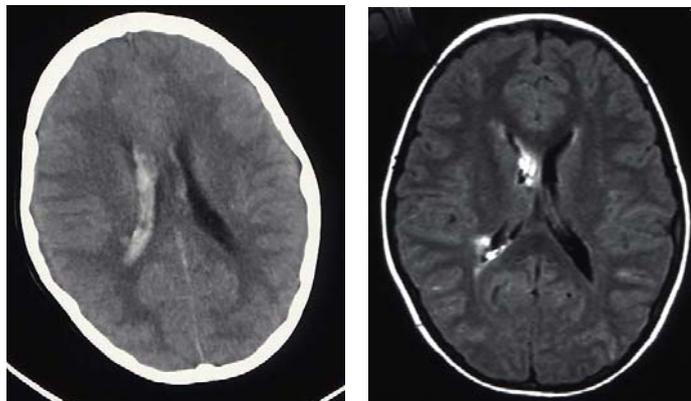
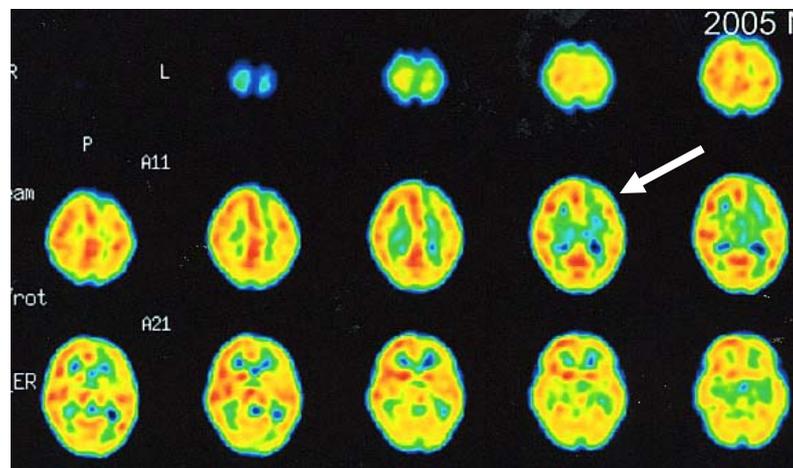


Fig. 3 (A)(B)



(C)



(D)



Table Summary of the cases

Pt. No.	Age(y) /Sex	Past History	Onset	Infarct on MRI	Angiographic Staging	Regional CBF on SPECT	Subsequent Infarction	Revascularization Surgery	Follow-up (month)
1	7/F	-	ICH(L)	-	(R)2,(L)3	normal	-	-	28
2	7/F	-	ICH(R),IVH	-	(R)3,(L)1	(R)decreased	+(Bil)	+(R)	20
3	9/F	TIA	ICH(R),IVH	-	(R)2,(L)3	(L)decreased	+(L)	+(L)	15