

Incidence and clinical feature of symptomatic cerebral hyperperfusion syndrome following vascular reconstruction

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Short title: Cerebral hyperperfusion syndrome following vascular reconstruction

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Abstract

Background: Vascular reconstructions are established treatment for ischemic cerebrovascular disease. Cerebral hyperperfusion syndrome (CHS) is occasionally seen following vascular reconstruction and manifest clinical symptom. The purpose of the present study is to investigate incidence and clinical feature of CHS following vascular reconstruction.

Methods: One hundred and forty four patients with ischemic cerebrovascular disease [53 carotid endarterectomy (CEA) for carotid artery stenosis, 48 carotid artery stenting (CAS) for carotid artery stenosis, 20 bypass surgery for atherosclerotic cerebrovascular disease, 40 bypass surgery for moyamoya disease (MMD)] underwent vascular reconstruction. Patients were examined neurologically and radiologically including CT, MRI and single photon emission tomography, and then CHS was evaluated.

Results: CHS developed in one (1.9%) CEA, one (2.1%) CAS, one (5.0%) bypass surgery for atherosclerotic cerebrovascular disease, and 6 (15.0%) bypass surgery for MMD. The incidence of CHS was significantly higher in patients with MMD. Aged patient and impairment of cerebrovascular reserve were correlated with CHS. Patients manifested disorientation following CEA and complained headache following CAS. Diffuse hemispheric hyperperfusion was detected by SPECT. Whereas, MMD patients manifested focal neurologic deficit, focal cerebral edema, and increased regional cerebral blood flow around vascular anastomosis. These patients were treated with blood pressure control and administration of free radical scavenger, and recovered without permanent

deficit.

Conclusions: The incidence of CHS is significantly higher in patients with MMD and results in vasogenic edema visible on MRI.

Introduction

Various vascular reconstructions have been developed to treat ischemic cerebrovascular disease. The efficacy of carotid endarterectomy (CEA) for carotid artery stenosis was proved with randomized study. Recently, carotid artery stenosis (CAS) has been widely performed especially in CEA high-risk patients. Most complications following CEA are ischemic in nature due to either embolization or inadequate cerebral protection in patients with a poor collateral supply. However, postoperative neurologic dysfunction can also be related to cerebral hyperperfusion, which is defined as major increase in ipsilateral cerebral blood flow (CBF) well above the metabolic demands of the brain tissue following the repair of carotid artery stenosis. This condition is termed as cerebral hyperperfusion syndrome (CHS), characterized by unilateral headache, face and eye pain, seizures, and focal symptoms related to cerebral edema or intracranial hemorrhage (21). Although the prognosis for patients with intracranial hemorrhage is poor, the incidence is relatively low (0.4-1.8%) (16,19). 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. Although the efficacy of superficial temporal artery (STA) - middle cerebral artery (MCA) anastomosis for atherosclerotic cerebrovascular disease have been controversial, it is considered as first line surgery for MMD (15). Recently, it is reported that focal hyperperfusion could occur after STA-MCA anastomosis and cause temporary neurological deterioration (6, 18, 22). The purpose of the present study is to investigate

incidence and clinical features of CHS following vascular reconstruction.

Material and Methods

From April 2004 to March 2009, we surgically treated one hundred and forty four patients with ischemic cerebrovascular disease. CEA and CAS were performed for the 53 sides of 52 patients, 48 sides of 46 patients, respectively. STA-MCA anastomosis was performed for the 20 sides of 20 patients with atherosclerotic cerebrovascular disease. STA-MCA anastomosis with encephalo-myo-synangiosis (EMS) was performed for the 40 sides of 26 patients with MMD. Preoperatively, the ischemic lesions were evaluated with CT and MRI, including diffusion-weighted image (DWI), fluid attenuated inversion recovery (FLAIR) image, T1-weighted image and T2-weighted image. CBF was evaluated with ¹²³I- iodoamphetamine single photon emission tomography (SPECT) with/without acetazolamide administration for cerebrovascular reserve (CVR). CVR was calculated using the following formula:

$$\text{(acetazolamide challenging SPECT count - resting SPECT count) / resting SPECT count} \\ (\%)$$

The CEA and bypass surgery were performed under general anesthesia and those who showed severe hypoperfusion with preoperative SPECT were treated with prolonged barbiturate or propofol sedation postoperatively. CAS was done under local anesthesia. Postoperative neurological signs were evaluated daily. Ischemic or hemorrhagic lesions were evaluated with CT on postoperative day 1. Thus, CBF was

evaluated with SPECT. When patients were complicated with neurological deterioration, MRI including DWI, FLAIR image were additionally performed. The patency of vascular reconstruction was confirmed by MR angiography or CT angiography.

The diagnostic criteria for symptomatic CHS includes all of the following issues; [1] the presence of neurologic signs including focal neurologic deficit and/or severe headache because of hemorrhagic changes; [2] patent surgically treated carotid artery or apparent visualization of STA-MCA bypass by angiography, and the absence of any ischemic changes by DWI; [3] postoperative increase in CBF in the ipsilateral hemisphere exceeding the flow in the contralateral hemisphere; and [4] the absence of other pathologies such as compression of the brain surface by the temporal muscle inserted for indirect pial synangiosis, ischemic attack, and seizure.

When CHS developed, these patients were treated with blood pressure control using calcium channel antagonist and administration of free radical scavenger, edaravone.

Perioperative vital sign parameters and CBF on SPECT were reviewed and correlation with CHS was investigated.

For statistical analysis, difference between groups were examined by Mann-Whitney's U test using jmp 6.0 (SAS institute Inc, Cary, NC). Statistical significance was accepted at $p < 0.05$.

Result

CHS developed in one (1.9%) CEA for carotid artery stenosis, one (2.1%) CAS for carotid artery stenosis, one (5.0%) bypass surgery for atherosclerotic cerebrovascular disease, and 6 sides (15.0 %) of bypass surgery for MMD. The incidence of CHS was significantly higher in patients with MMD. In these patients, patency of treated ICA or STA-MCA bypass were confirmed in all these patients by angiography during follow-up period. Postoperative MRI showed no ischemic changes and SPECT revealed focal intense increase in CBF at the side of revascularization.

The patients with CHS were summarized in Table 1. The patient manifested disorientation and headache following CEA and CAS, respectively. The symptom appeared postoperative 2nd to 4th day and lasted about five days. Intracerebral hemorrhage was detected by CT after CAS at the site of the previous cerebral infarction. Diffuse hemispheric hyperperfusion was detected by SPECT. Symptoms were relieved by intensive blood pressure control with the use of free radical scavenger and these patients did not have permanent neurologic deficit or delayed neurologic deterioration during follow-up period.

The MMD patients manifested focal neurologic deficit (fluctuating aphasia, numbness in the contralateral side of the face and upper limb, facial palsy, and dysarthria). All of them were female and adult. Four cases were ischemic onset and two cases were hemorrhagic onset. The symptom of CHS appeared postoperative 2nd to 6th day and lasted one to ten days. Imaging studies revealed focal cerebral edema and increased regional CBF around vascular anastomosis. MRI showed focal cerebral edema and

SPECT demonstrated increase of regional CBF around vascular anastomosis. These patients were treated with blood pressure control and administration of free radical scavenger and recovered without permanent deficit.

The characteristic of patient with and without CHS were listed in Table 2. In MMD, adult patient and CVR impairment were significantly correlated with CHS.

Case presentation

Patient 1

A 75-year-old man, who had a history of transient ischemic attack, referred to our hospital for treatment of right ICA severe stenosis. MRI showed chronic ischemic lesion in the bilateral white matter (Fig. 1A). CT angiography revealed severe stenosis at the origin of the right ICA (Fig. 1B). SPECT showed mild hypoperfusion of the right cerebral hemisphere (49 ml/100g/min) and impairment of the CVR (1%) (Fig. 1C, D). CEA was performed under general anesthesia. The patient showed no neurologic deficit immediately after surgery. On postoperative day 2, disorientation appeared and he became restless. DWI showed no evidence of ischemic change (Fig. 1E). CT angiography revealed satisfactory widening of the stenosis (Fig. 1F). Hemispheric hyperperfusion was revealed by SPECT (59 ml/100g/min) (Fig. 1G). Intensive blood pressure control and the use of free radical scavenger relieved his symptoms that completely disappeared 6 days after surgery. The hyperperfusion was improved in the SPECT examined on the postoperative day 8 (Fig. 1H).

Patient 4

A 36-year-old woman, who had a history of left intracerebral hemorrhage, referred to our hospital for treatment of right cerebral hypoperfusion due to MMD. She was neurologically intact despite history of intracerebral hemorrhage. MRI showed old cerebral hemorrhage at the left corona radiata (Fig. 2A). Angiography showed right internal carotid artery (ICA) stenosis and left MCA stenosis. Moyamoya vessels were developed bilaterally (Fig. 2B). SPECT showed right hypoperfusion (46 ml/100g/min) (Fig. 2C) and acetazolamide challenge demonstrated steal phenomenon on the right side (CVR; -7%). STA-MCA with EMS was performed for the right side without difficulty. Postoperatively, the patient awakened from anesthesia without neurological deficit and CT demonstrated no new lesion. However, on postoperative day 3, dysarthria appeared. Right cerebral cortex was slightly high-intensity on the FLAIR image (Fig. 2D). DWI showed no ischemic lesion (Fig. 2E). MR angiography showed the apparently patent STA-MCA bypass. SPECT demonstrated increased CBF around anastomosis site (57 ml/100g/min) (Fig. 2F). She was diagnosed as CHS and treated with free radical scavenger. On postoperative day 11, FLAIR image demonstrated progression of high intensity lesion in the right side cerebral cortex and sulcus (Fig. 2G) and focal hyperperfusion was detected by SPECT (Fig. 2H). On postoperative day 13, neurological signs were relieved. One month later, MRI findings returned to normal and the CBF was normalized (Fig. 2I, J).

Patient 5

A 57-year-old woman, who had a history of left occipital infarction, referred to our

hospital for treatment of cerebral hypoperfusion due to MMD. Neurological examination revealed right homonymous hemianopsia. CT and FLAIR image demonstrated cerebral infarction in the left occipital lobe (Fig. 3A). Angiography showed bilateral ICA occlusion at the terminal portion accompanied with moyamoya vessels (Fig. 3B). SPECT showed hypoperfusion in the right temporal lobe (45 ml/100g/min) (Fig. 3C) and the response to the acetazolamide challenge was 0%. STA-MCA with EMS was performed for the right side without difficulty. The patient was neurologically well when she awoke from anesthesia and new lesion was not detected by CT. However, on postoperative day 2, left upper extremity numbness and dysarthria appeared without impairment of consciousness. SPECT demonstrated increased CBF around anastomosis site (62 ml/100g/min) (Fig. 3D). She was treated with free radical scavenger. On postoperative day 7, FLAIR image showed an area of mild hyperintensity in the right frontal lobe (Fig. 3E). An ischemic lesion was not apparent (Fig. 3F). Local cerebral hyperperfusion was still detected by SPECT (Fig. 3G). On postoperative day 9, her symptom improved. One month later, cerebral edema disappeared and cerebral blood flow was normalized (Fig. 3H, I).

Discussion

CHS following CEA or CAS

Systematic analyses of a large series of patents treated with CEA or CAS revealed that the incidence of CHS after CEA ranges from 0.4 to 1.8% and the incidence

of postoperative intracranial hemorrhage is approximately 0.6% (16, 19). Risk factors for this syndrome include long-standing hypertension, high-grade stenosis, poor collateral blood flow, and contralateral carotid artery occlusion, which often impair the cerebral hemodynamic reserve (16). In case of CEA, acute cerebral ischemia during clamping of the ICA may be associated with the development of post-CEA hyperperfusion (19). The onset of hyperperfusion peaked on the 6th postoperative day in those who had undergone CEA and within 12 hours in those who had undergone CAS (19). In our study, the incidence of CHS after CEA and CAS was 1.9% and 2.1% respectively, which were consistent with previous report (16, 19). Symptoms of CHS were disorientation in CEA patient and severe headache due to the minor cerebral hemorrhage in CAS patient. And these symptoms were relived about one week later. Diffuse hemispheric hyperperfusion was detected by SPECT. Patient 2 complicated with intracerebral hemorrhage at the site of the previous cerebral infarction. Patients who had preexisting previous stroke were at a high risk of developing CHS (7). Although we reviewed CHS risk factors (carotid artery stenosis grade, contralateral artery stenosis), no one was significantly correlated with CHS because of low number of CHS (data not shown).

CHS in MMD

Several authors have reported temporary neurologic deterioration due to the hyperperfusion after revascularization surgery in patients with MMD (6, 18, 22). It is reported that the incidence of the CHS is 10-20% and adult-onset or hemorrhagic-onset patients had significantly higher risk of CHS (3, 4, 8, 20). In our study, CHS were

recognized in 6 of 40 sides (15.0%) and all of them were adult. This frequency corresponds well with recent reports. In terms of onset, two cases were hemorrhagic onset, but the sides of CHS were contralateral side of hemorrhage. Therefore, relation with hemorrhagic onset and CHS is not clear. The clinical signs of CHS of our 6 MMD patients was characterized by fluctuating aphasia, numbness in the contralateral side of the face and upper limb, facial palsy, and dysarthria, in accordance with the anatomical location of the site of anastomosis. Neurological deficits were usually observed one week or less after surgery, and resolved within 2 weeks. As previous reports, FLAIR image showed hyperintensity lesion around anastomosis site (14). We considered the lesion as vasogenic edema, since it is high intensity FLAIR image or T2-weighted image and no signal change on DWI. The lesion was predominant in cortex rather than in white matter. Thus, Cho et al (1) reported gadolinium enhancement of subarachnoid space on FLAIR image after carotid revascularization, indicating blood-brain barrier disruption. This phenomenon may result in delayed intracerebral hemorrhage (5). SPECT revealed focal relative hyperperfusion area, against with hemispheric hyperperfusion of CEA or CAS. CHS can be seen following bypass surgery for atherosclerotic cerebrovascular disease (13). Yamaguchi et al (23) reported the incidence of CHS as 6% (3/50) in those patients, consistent with this study (5%).

Mechanism of CHS in MMD

The hypoperfusion status of MMD is different from that of carotid artery stenosis. Collateral from anterior communicating artery or posterior communicating

artery may develop in carotid artery stenosis. On the other hand, stenosis occur at the terminal portion of ICA in MMD, and the blood flow is mainly supplied from moyamoya vessels. At surgery of MMD, preexisting cortical branches of middle cerebral artery are atrophic and neovascularization is apparent. In fact, CVR was impaired in the CHS positive group in this study. Thus, adult patient was correlated with CHS. STA is relatively larger in adult patient and the blood flow from STA result in focal perfusion mismatch even in low-flow bypass. Against atherosclerotic disease, MMD is dominantly seen in female. Therefore, hormonal function may be a cause of development of CHS. Lastly, microbleeds is frequently detected in MMD brain (12). That indicates brain tissue itself as well as microvessels had been affected and become fragile.

Detection of CHS

Once an intracerebral hemorrhage or subarachnoid hemorrhage occurs, serious morbidity or mortality may follow. Therefore, it is very important to predict the sign of CHS and prevent it. First, neurologic deficit such as dysarthria or motor aphasia should be carefully examined especially in patients with MMD. And MRI is useful to detect edematous lesion at the early stage as shown in Fig. 2D. Sometimes MRI finding precede the neurological signs. Routine CBF measurement is recommended for accurate diagnosis of postoperative hyperperfusion. We usually employ SPECT 48-72 hours after vascular reconstruction. It is a sensitive method for recognizing CHS, differentiating between ischemia and hyperperfusion. Iwata et al examined transcranial Doppler sonography within 3 hours after CAS and reported the MCA mean flow velocity were

significant predictor of CHS (10).

Management of CHS

CHS must be treated carefully, as treatment of hyperperfusion is opposite to that for postoperative ischemia. In such patients, cerebrovascular autoregulation is impaired, and the CBF may be dependent on blood pressure. In fact, postoperative blood pressure was relatively higher in CHS positive group as shown in Table 2. Additionally, postoperative control of the blood pressure was significantly associated with the development of intracranial hemorrhage in patients with CHS after CEA (19). Therefore, systemic arterial pressure must be strictly controlled to within the normal or lower range. Thus, reactive oxygen species produced by reperfusion may play a role in the pathogenesis of hyperperfusion (2). Free radical scavenger was reported to prevent CHS after CEA in patients with atherosclerotic occlusive disease (17). When predominant cerebral edema is accompanied, osmotic diuretics such as glycerol may be effective. Finally, barbiturate or propofol sedation therapy may be induced for severe hyperperfusion to prevent hemorrhagic complication.

Prognosis of CHS

The mortality and morbidity rates in patients with postoperative CHS were significantly higher in patients with intracranial hemorrhage than in those without (19). Presumably, the neurological deficits in those without hemorrhage are reversible (20). However, recent studies have demonstrated that asymptomatic cerebral hyperperfusion is

often detected on CBF imaging and impairs cognitive function (10). Further examination including mental function is needed.

Limitation

Positron emission tomography is not available in our institute. Since it has been reported that CVR is correlated with positron emission tomography parameters (9), we employed SPECT to evaluate CBF and CVR. This study is retrospective study and the incidence of CHS was influenced with some treatment. Thus, some of the treatment is no known value or at least there is no level 1 evidence to support eg. sedating the patient after surgery, edaravone, calcium blockers.

Conclusions

CHS was significantly frequent after revascularization for MMD. Aged patient and impairment of cerebrovascular reserve were correlated with CHS. MRI showed focal vasogenic edema and SPECT demonstrated increase of regional CBF around vascular anastomosis. Neurological deficits in those without hemorrhage were reversible and the finding of imaging studies returned to normal.

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Figure legends**Fig. 1 Patient 1**

A: Preoperative MRI (fluid attenuated inverted recovery; FLAIR image) shows ischemic lesion in the bilateral deep white matter.

B: CT angiography shows severe stenosis at the origin of the right internal carotid artery (arrow).

C: Preoperative single photon emission tomography (SPECT) shows reduction in right hemispheric perfusion (arrow).

D: SPECT with acetazolamide shows severe impairment of cerebrovascular reserve (arrow).

E: MRI (diffusion-weighted image; DWI) two days after surgery shows no ischemic lesion.

F: Postoperative CT angiography shows satisfactory widening of the stenosis (arrow).

G: SPECT 2 days after CEA demonstrates diffuse hyperperfusion in the right cerebral hemisphere (arrow).

H: SPECT one month after surgery shows disappearance of focal hyperperfusion.

Fig. 2 Patient 4

A: Preoperative MRI (FLAIR image) shows old hemorrhage in the left basal ganglia (arrow).

B: Angiography shows bilateral steno-occlusive lesion of internal carotid arteries with

moyamoya vessels.

C: SPECT shows hypoperfusion dominantly in the right side.

D: MRI (FLAIR image) on postoperative day 3, demonstrates an area of mildly high intensity along with right frontal cortex (arrow).

E: MRI (DWI) shows no ischemic lesion.

F: SPECT on postoperative day 3 demonstrates focal relative hyperperfusion area in the right frontal lobe corresponding to the hyperintense is on MRI (arrow).

G: MRI (FLAIR image) on postoperative day 11 demonstrates an area of high intensity in the right frontal cortex to subarachnoid space (arrow).

H: SPECT on postoperative day 11 shows localization of hyperperfusion around anastomosis site (arrow).

I: MRI (FLAIR image) one month after surgery shows normalization of the high intensity lesion.

J: SPECT one month after surgery shows disappearance of focal hyperperfusion.

Fig. 3 Patient 5

A: Preoperative MRI (FLAIR image) shows old infarction in the left occipital lobe (arrow).

B: Cerebral angiography delineates steno-occlusive changes the terminal portions of the bilateral internal carotid arteries, and abnormal network-like vessels are apparent at the bilateral basal ganglia.

C: SPECT shows hypoperfusion dominantly in the right side.

D: SPECT 2 days after surgery demonstrates relatively diffuse hyperperfusion in the right side.

E: MRI (FLAIR image) 7 days after surgery demonstrates an area of high intensity in the right frontal cortex (arrow).

F: MRI (DWI) 7 days after surgery shows no ischemic lesion.

G: SPECT 7 days after surgery demonstrates focal hyperperfusion in the right side (arrow).

H: MRI (FLAIR image) one month after surgery shows normalization of the high intensity lesion.

I: SPECT one month after surgery shows disappearance of focal hyperperfusion.

A

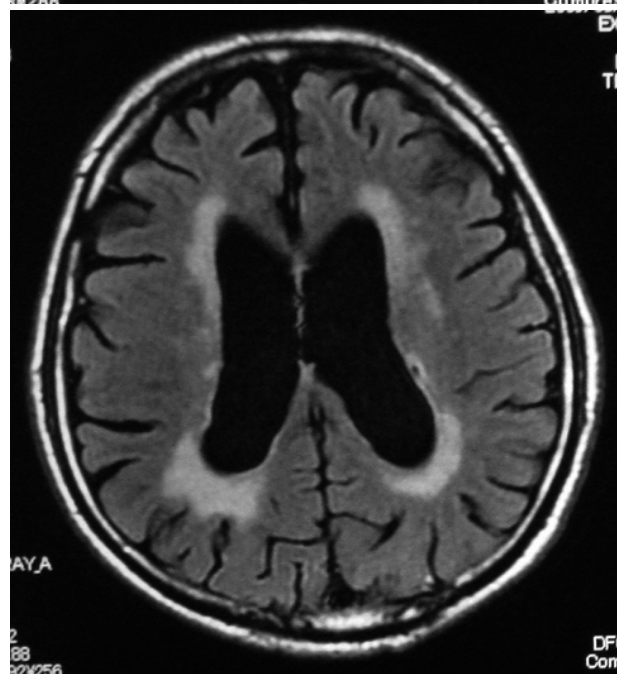
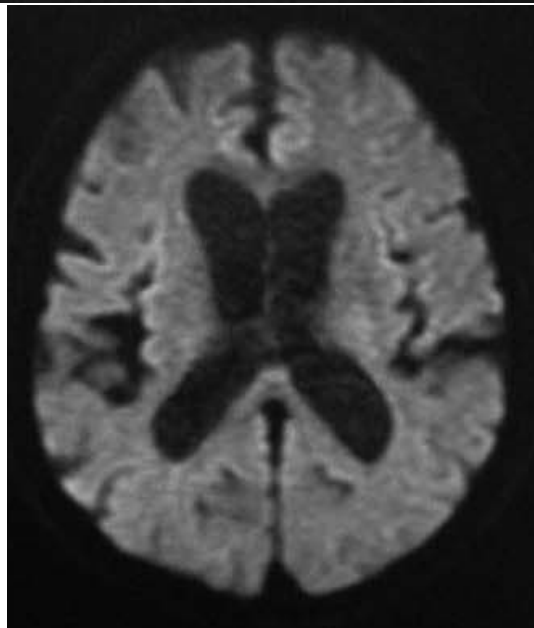
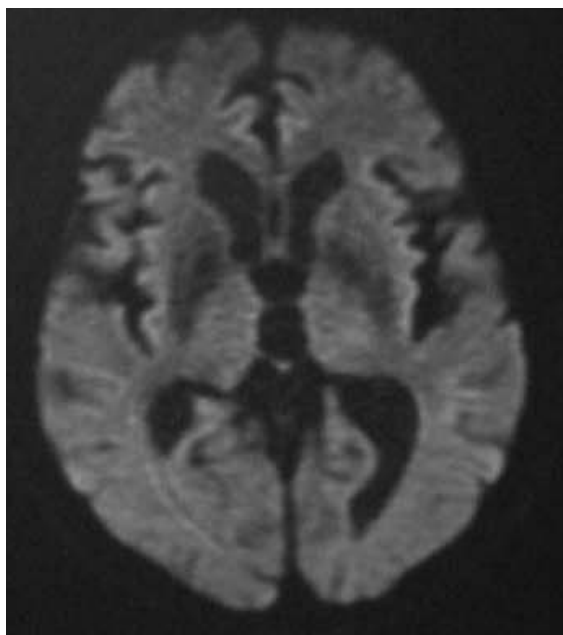
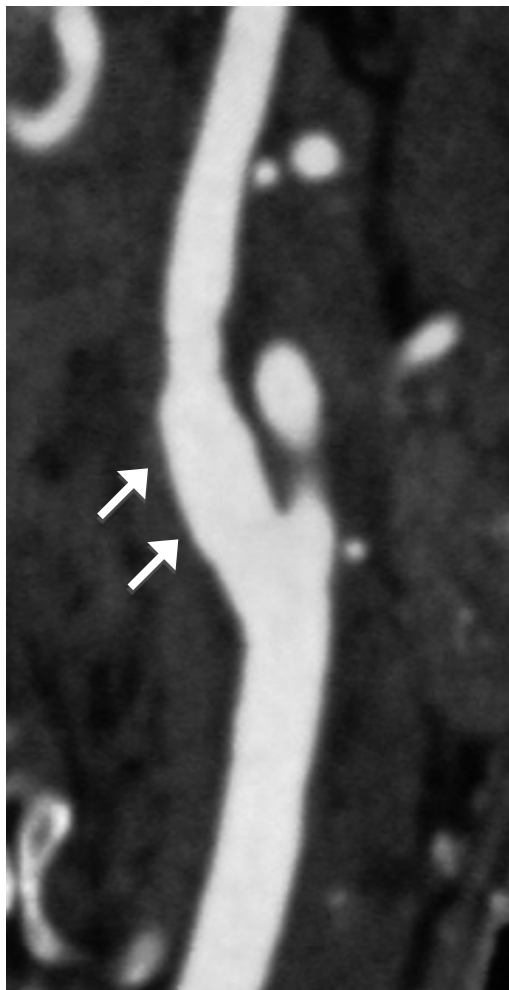


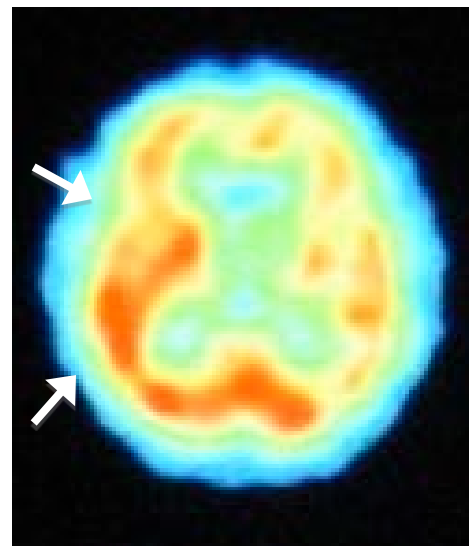
Fig. 1 E



F



G



H

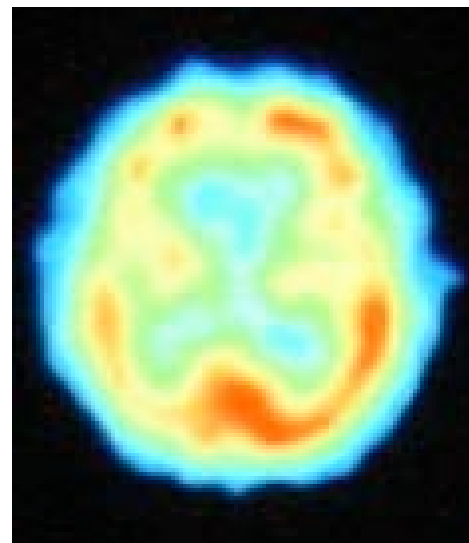
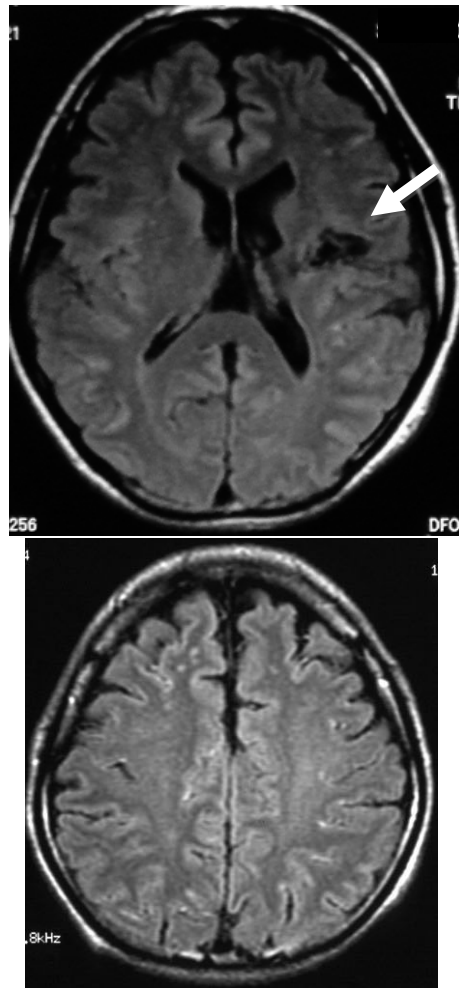
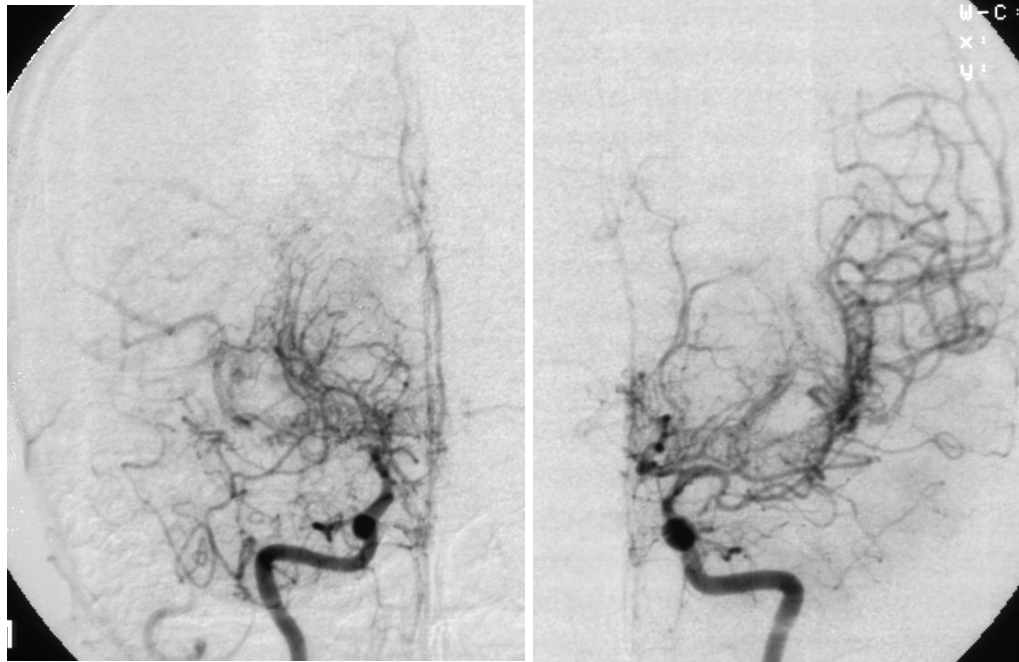


Fig. 2

A



B



C

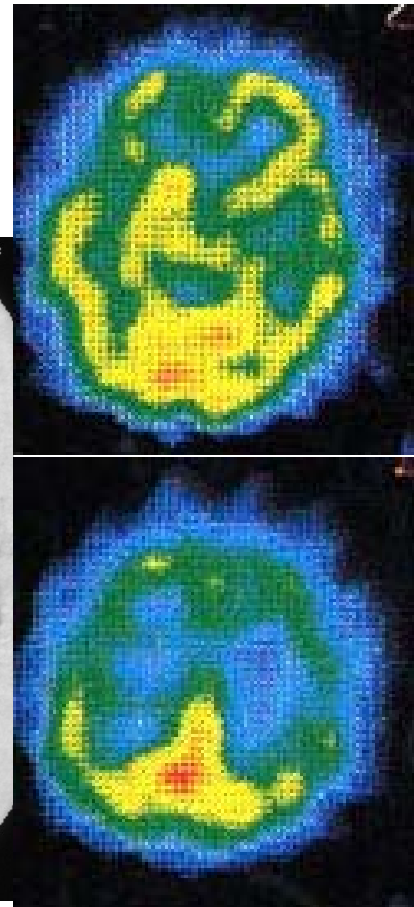


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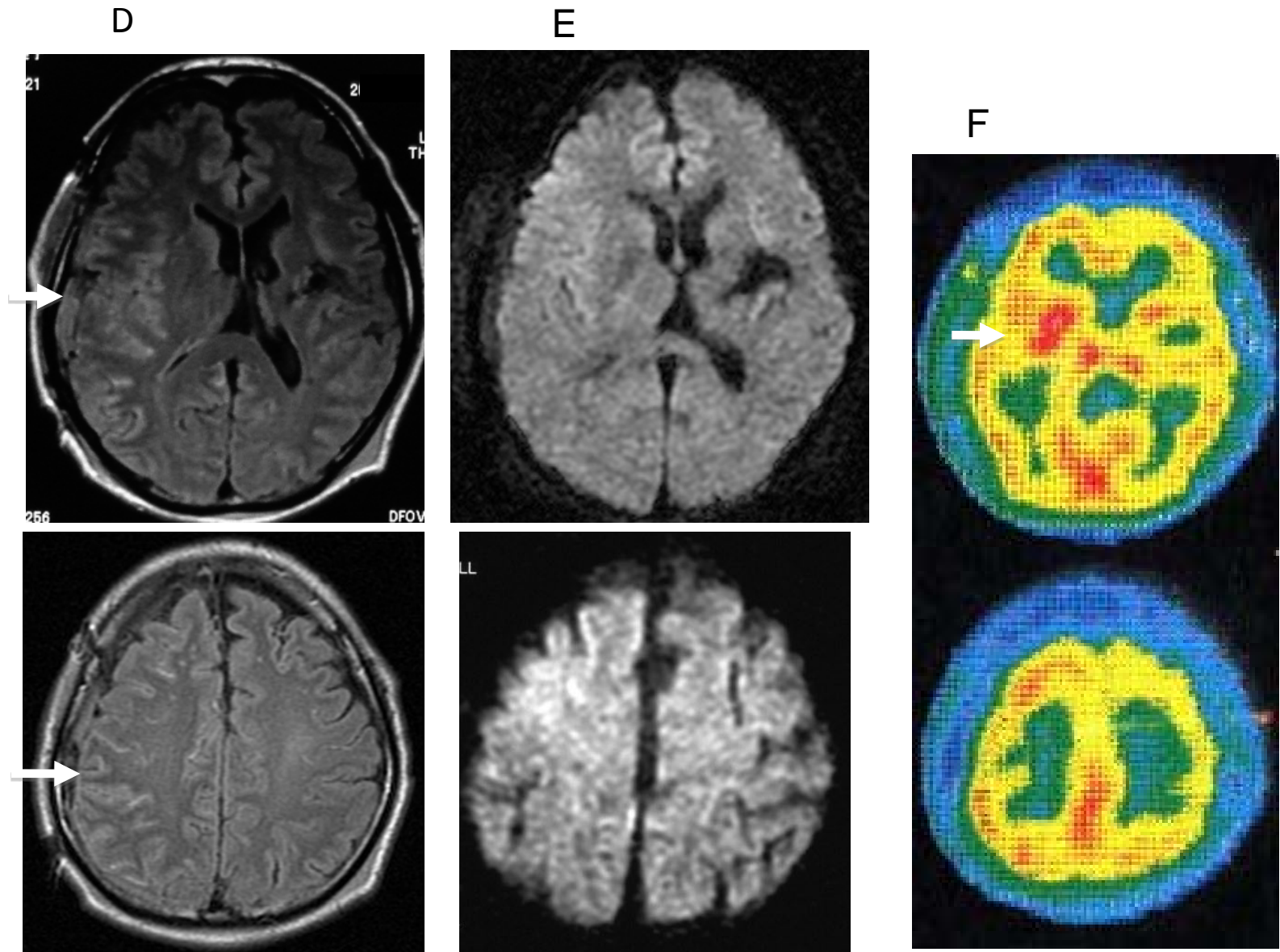


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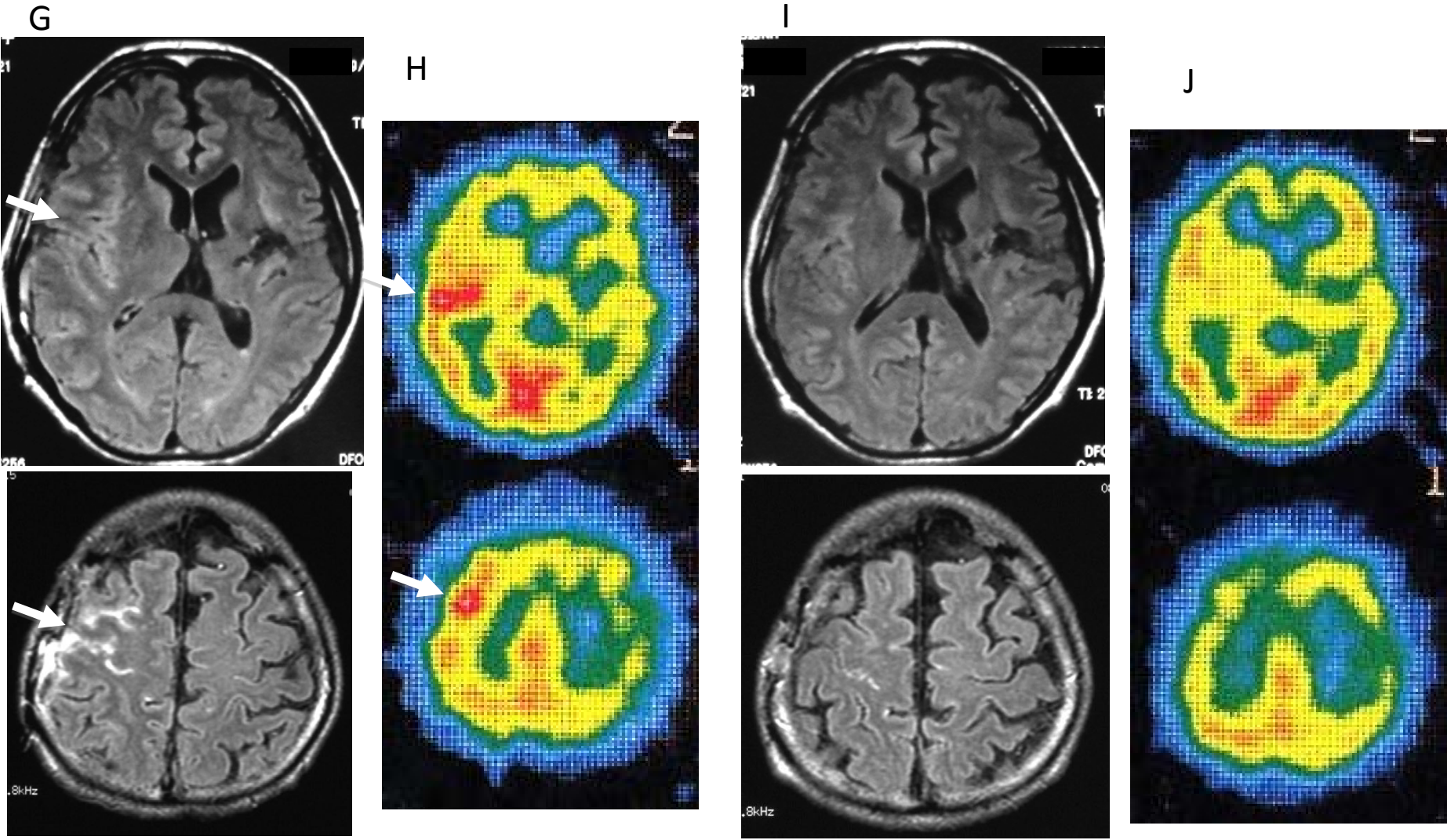
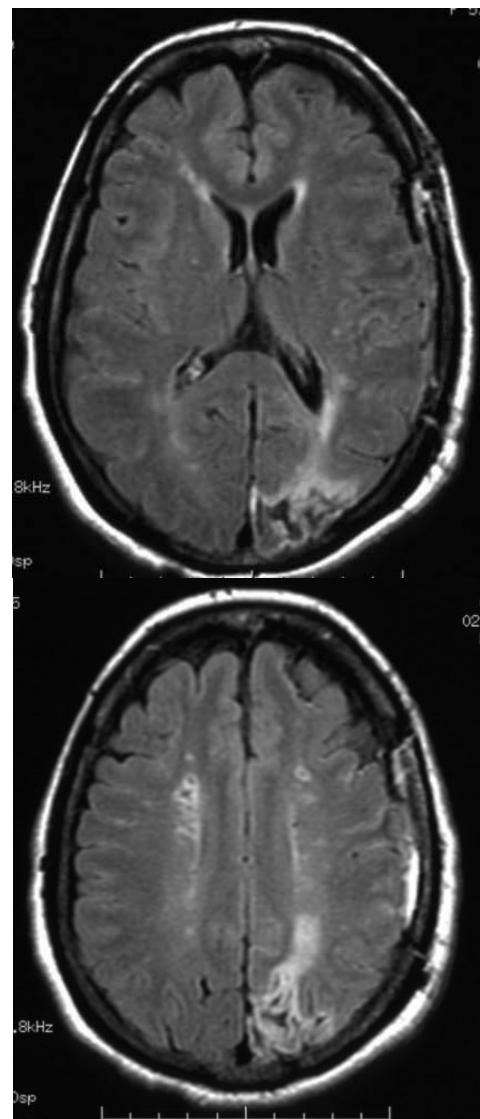
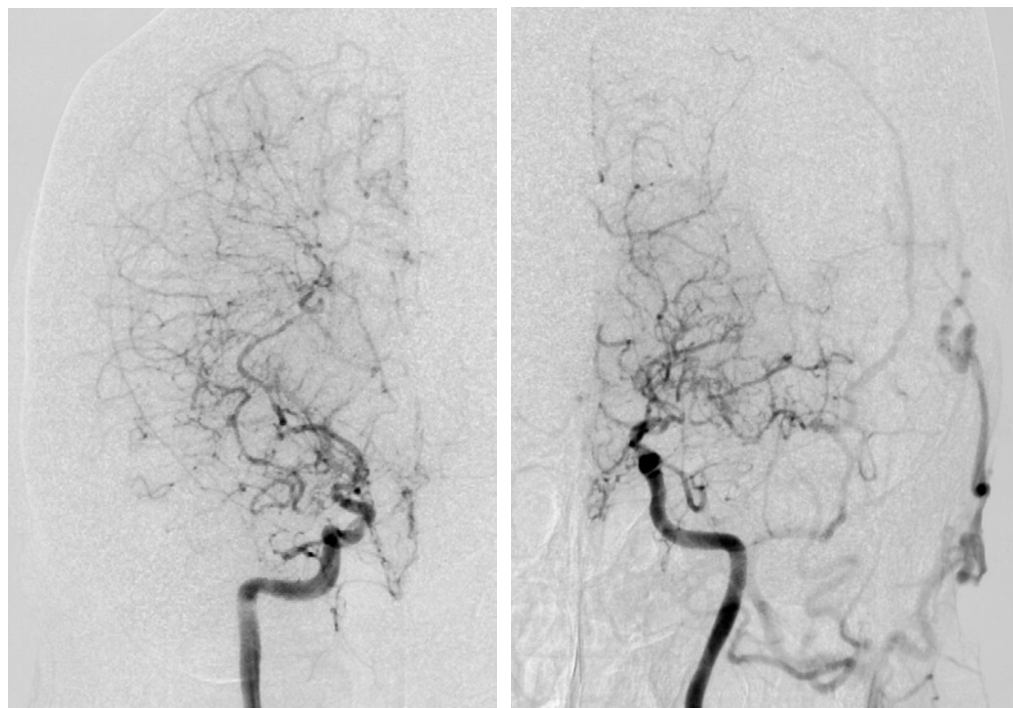


Fig. 3

A



B



C

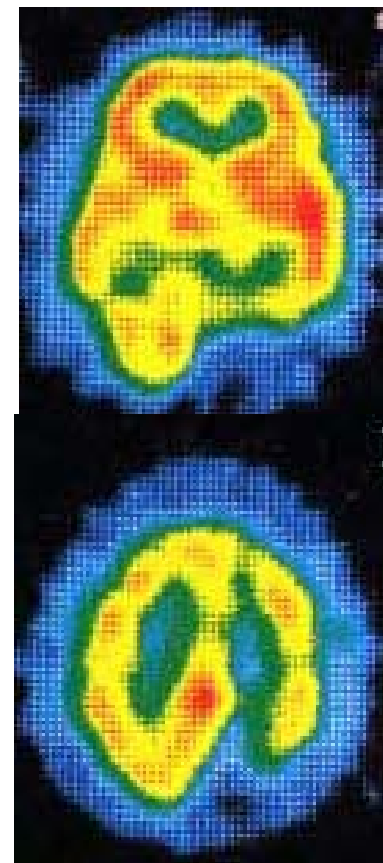
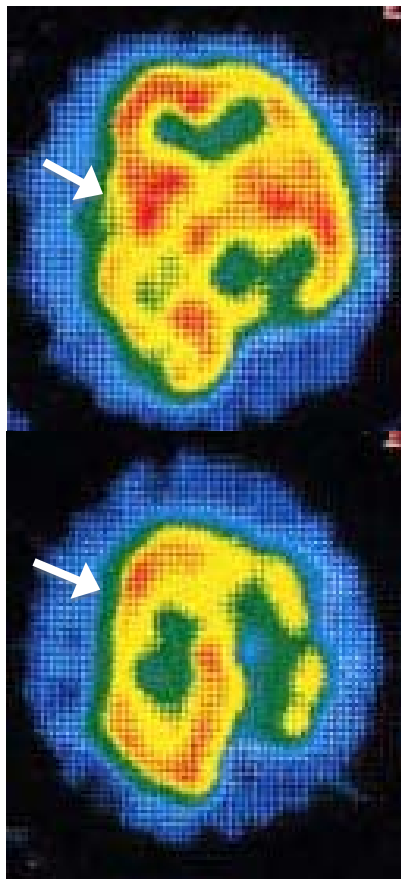
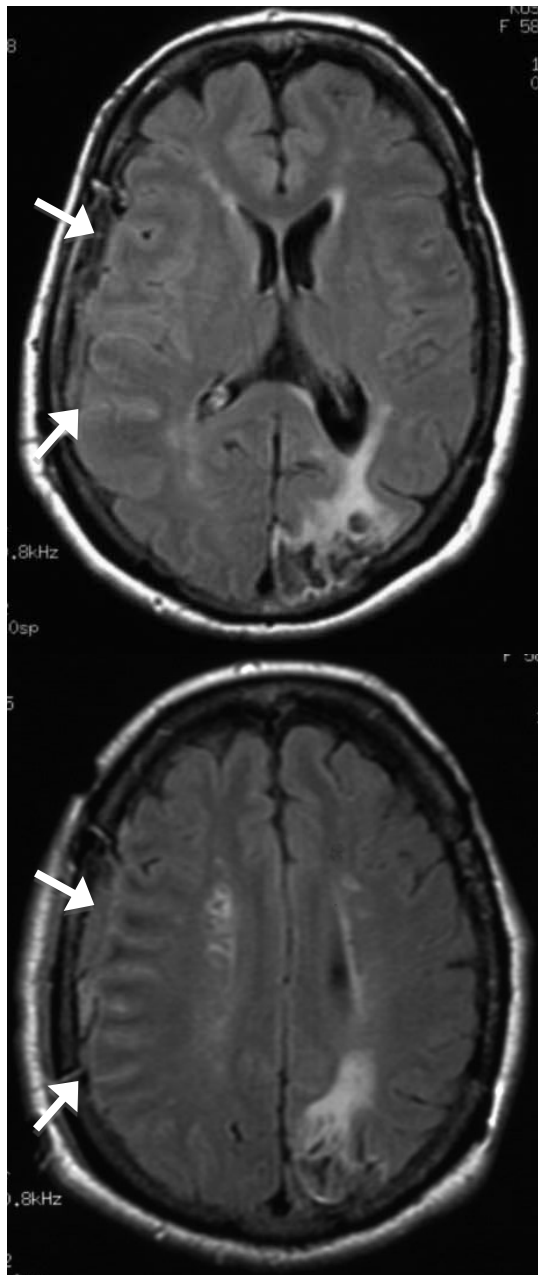


Fig. 3

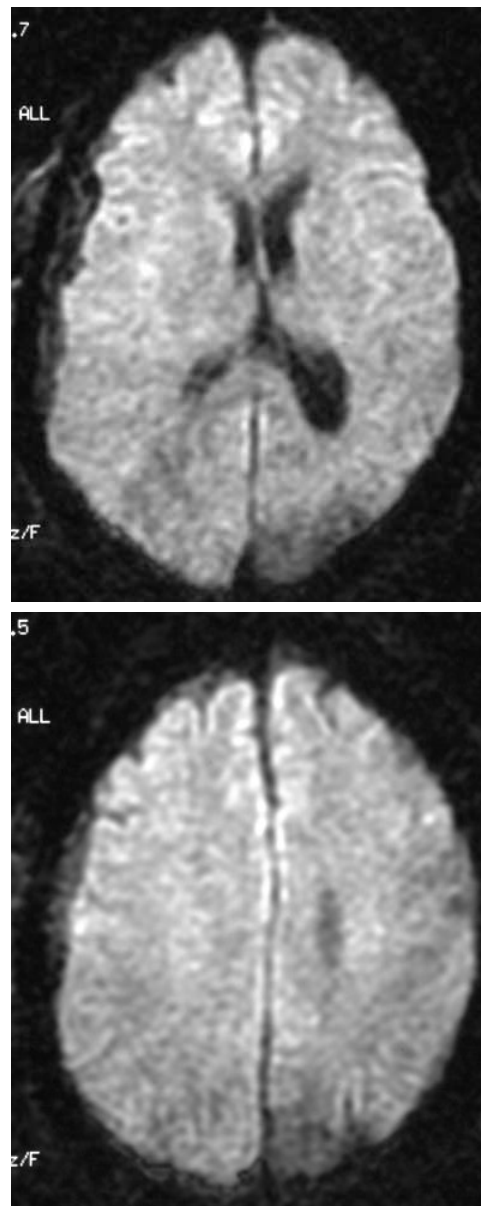
D



E



F



G

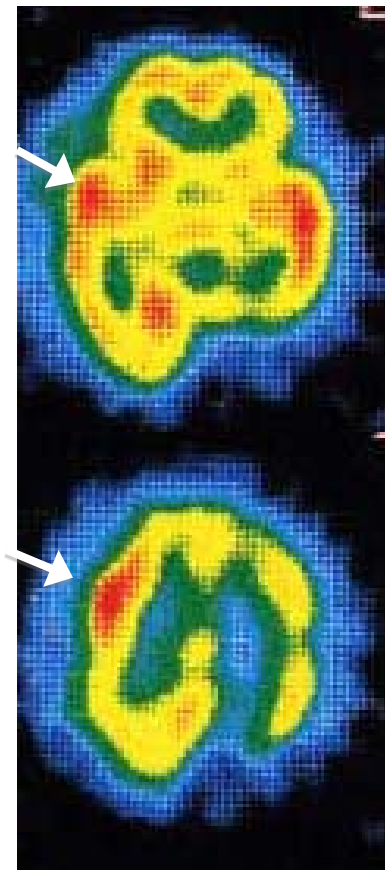
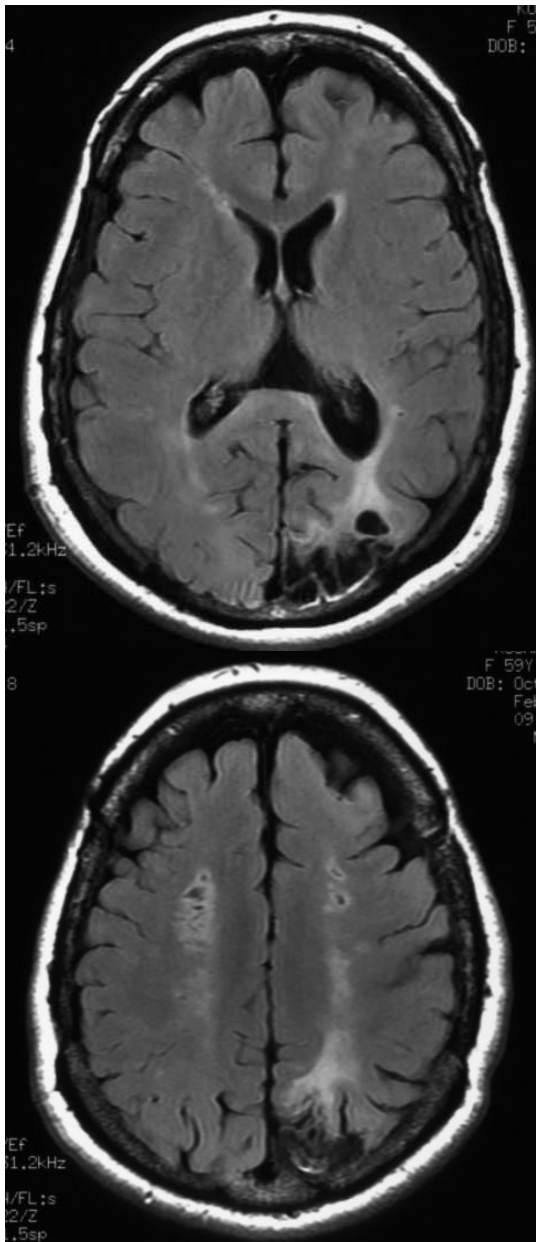


Fig. 3

H



I

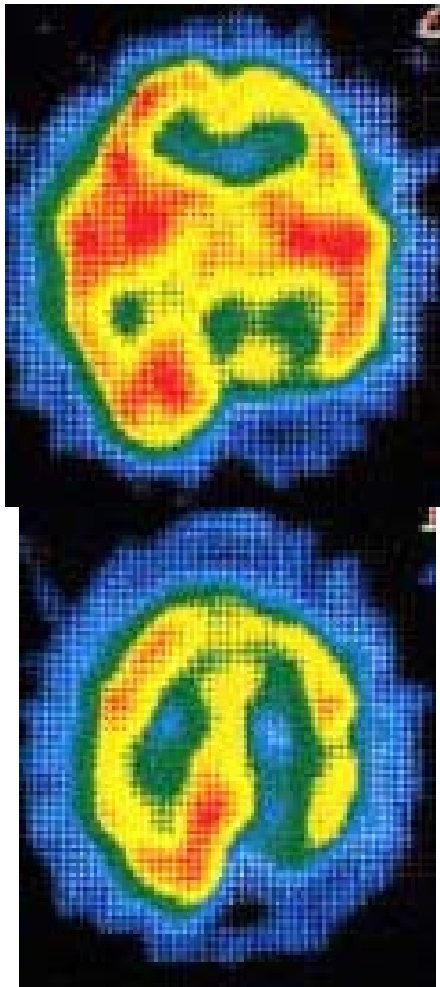


Table 1 Summary of cerebral hyperperfusion syndrome following vascular reconstruction

Patient	Treatment	Age/Sex	Onset side	Treated side	Sign of hyperperfusion	Duration (days)	Area
1	carotid endarterectomy	75/M	TIA right	right	disorientation	2-6	diffuse
2	carotid artery stenting	69/F	infarction left	left	headache ICH	4-10	diffuse
3	STA-MCA anastomosis	68/M	TIA right	right	disorientation dysarthria	3-7	focal
4	moyamoya disease	36/F	ICH left putamen	right	dysarthria	3-13	focal
5	moyamoya disease	57/F	infarction left occipital	right	left numbness dysarthria	2-9	focal
6	moyamoya disease	43/F	ICH left subcortex	right	facial palsy dysarthria	6-11	focal
7	moyamoya disease	29/F	TIA left	left	right numbness motor aphasia	6-7	focal

8	moyamoya disease	25/F	loss of consciousness	right	headache	2-6	focal
				left	dysarthria	3-8	focal

F: female

ICH: intracerebral hemorrhage

M: male

STA-MCA: superficial temporal artery-middle cerebral artery

TIA: transient ischemic attack

Table 2 Characteristics of patient with and without CHS

	CHS (-)	CHS (+)	Statistics
CEA (53 side)	52	1	
Male/female	49/3	1/0	NS
Age (y.o.)	68.3	75	NS
Preop BP (mmHg)	131.6/71.6	122/82	NS
Postop BP(mmHg)	122.3/73.3	147/99	NS
CBF (ml/100g/min)	36.9	53	NS
CVR (%)	5.6	5	NS
CAS (48 side)	47	1	
Male/female	44/3	0/1	NS
Age (y.o.)	72.5	69	NS
Preop BP (mmHg)	132.6/75	121/62	NS
Postop BP(mmHg)	110.6/61.2	125/66	NS
CBF (ml/100g/min)	33.5	46	NS
CVR (%)	20.4	24	NS
STA-MCA bypass (20 side)	19	1	
Male/female	18/1	1/0	NS
Age (y.o.)	63.3	68	NS
Preop BP (mmHg)	131.7/75.7	122/63	NS
Postop BP (mmHg)	146.5/87	135/72	NS
CBF (ml/100g/min)	28.8	35	NS
CVR (%)	5.5	17	NS
Moyamoya (40 side)	34	6	
Male/female	10/24	0/6	NS
Age (y.o.)	18.6	30.8	P<0.01
Preop BP (mmHg)	128.3/71.4	124.3/77.5	NS
Postop BP (mmHg)	118.6/62.9	140/76.7	NS
CBF (ml/100g/min)	45.3	49	NS
CVR (%)	17.8	3.7	P<0.05

CHS; cerebral hyperperfusion syndrome

CEA; carotid endarterectomy

Preop BP; preoperative blood pressure (systolic mmHg/diastolic)

Postop BP; postoperative blood pressure (systolic mmHg /diastolic)

CBF; cerebral blood flow

CVR; cerebral vascular reserve

CAS; carotid artery stenting

STA-MCA bypass; superficial temporal artery - middle cerebral artery bypass

NS; not significant