



Published in final edited form as:

J Neurol Sci. 2010 September 15; 296(1-2): 115–120. doi:10.1016/j.jns.2010.06.003.

Capsular Warning Syndrome Caused By Middle Cerebral Artery Stenosis

Jun Lee, MD^{a,b)}, Gregory W Albers, MD^{a)}, Michael P Marks, MD^{c)}, and Maarten G Lansberg, MD, PhD^{a)}

^{a)}Department Neurology and Neurological Sciences and the Stanford Stroke Center, Stanford University Medical Center, Stanford, CA, USA

^{b)}Department of Neurology and Stroke Center, Yeungnam University Medical Center; Daegu, South Korea

^{c)}Department of Radiology and the Stanford Stroke Center, Stanford University Medical Center, Stanford, CA, USA

Abstract

The capsular warning syndrome is a term used to describe recurrent stereotyped lacunar transient ischemic attacks (TIAs). This syndrome is associated with a high risk of developing a completed stroke. The presumed mechanism for this syndrome is angiopathy of a lenticulostriate artery. We describe the case of a 33-year-old man who presented with the capsular warning syndrome who was successfully treated with angioplasty. The patient's capsular warning syndrome manifested as recurrent episodes of transient left hemiparesis. Symptoms recurred one to three times daily despite treatment with antithrombotics. Cerebral angiography demonstrated stenosis of the right middle cerebral artery (MCA) with decreased flow to a dominant lenticulostriate artery.

Angioplasty of the right middle cerebral artery increased flow to the lenticulostriate artery and the TIAs resolved following the procedure. In select cases intracranial angioplasty, may be an effective treatment for patients with capsular warning syndrome.

Keywords

Transient ischemic attack; Capsular warning syndrome; Angioplasty; balloon; Lenticulostriate disease; vascular; Middle cerebral artery occlusion; Cerebral angiography; Single-Photon Emission Computerized Tomography

© 2010 Elsevier B.V. All rights reserved.

*Address correspondence to Dr Lansberg Department of Neurology and Neurological Sciences, Stanford University Medical Center, 701 Welch Road, Suite 325, Palo Alto, CA 94304, USA; lansberg@stanford.edu Telephone number: 1-650-723-4499 Telefax number: 1-650-723-4451.

^{a)}Department of Neurology and Neurological Sciences, Stanford University Medical Center, 701 Welch Road, Suite 325, Palo Alto, CA 94304, USA

^{b)}Department of Neurology, Yeungnam University Medical Center, 317-1 Daemyungdong, Namku, Daegu, 705-717, South Korea

^{c)}Department of Radiology, Stanford Medical Center, 300 Pasteur Drive, Room S047, Stanford, CA 94305, USA

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Conflict of interest disclosure This study was supported by Yeungnam university research grants in 2009

Introduction

The risk of early completed stroke in patients with transient ischemic attacks (TIAs) has been reported to be 9.5 to 20% [1-5]. The risk is particularly high in patients with the “capsular warning syndrome”. In this population a 40% 10-day stroke risk has been reported [6]. Patients with the capsular warning syndrome exhibit stereotyped recurrent motor weakness [7]. Although various etiologies have been suggested, the mechanism believed to be the most common cause of the capsular warning syndrome is small perforating artery disease. Patients with this syndrome are therefore typically treated with antithrombotic agents to prevent recurrent events. We report a case of a patient who presented with a typical capsular warning syndrome in the setting of predominantly large artery disease. The patient had severe stenosis of the right middle cerebral artery (MCA) which impaired flow to a dominant lenticulostriate artery. Intracranial angioplasty resulted in improved flow to the lenticulostriate artery and resolution of the patient’s TIAs.

Case

A 33-year-old man developed sudden onset left hemiparesis and dysarthria lasting five minutes. He recovered spontaneously and did not seek medical care. One month after his initial episode he experienced a second similar episode for which he was evaluated in the emergency room. His neurological examination on admission was unremarkable. His past medical history is notable for chronic hepatitis C. There is no known history of hypertension, diabetes, hyperlipidemia, migraine, or heart disease. Brain magnetic resonance imaging (MRI) and magnetic resonance angiography (MR angiography) were notable for normal diffusion-weighted imaging without evidence of acute ischemia; a chronic small deep infarction adjacent to the lateral ventricle on fluid-attenuated inversion recovery (FLAIR) (Fig. 1A), and a focal stenosis of the right MCA. Perfusion MRI demonstrated an area in the right MCA territory with mildly delayed perfusion on time to peak perfusion maps (TTP), but with preserved blood volume on the cerebral blood volume map (Fig. 1B). Brain single photon emission computed tomography (SPECT) also showed decreased perfusion in the right MCA territory compared to the left. After injection with acetazolamide, blood flow increased consistent with preserved vascular reactivity in the cerebral cortex and there was a decrease in the vascular reserve in the deep hemisphere (Fig. 2A, 2B). Levels of serum total cholesterol, triglyceride, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol, and lipoprotein(a) were 124 mg/dL, 77 mg/dL, 28.7 mg/dL, 84.4 mg/dL, and 5.28 mg/dL, respectively. Anti-HCV antibody and HCV PCR were positive. Glycosylated hemoglobin level and urine analysis were within normal range. Antithrombin III level, protein C activity, protein S activity, serum homocysteine level, hs C-reactive protein level, and prothrombin time (PT) and partial thromboplastin time (PTT) were within normal range. Plasma fibrinogen level was decreased (142 mg/dL) and rheumatoid factor (RF) was 16.8 IU/mL. Anticardiolipin antibody, lupus anticoagulant, antinuclear antibody (ANA), and anti-double-stranded DNA (Anti-ds DNA) were normal. Cardiac evaluation including electrocardiography, transthoracic echocardiography, and transesophageal echocardiography was unremarkable.

During the patient’s hospitalization he experienced frequent episodes of left hemiparesis, left central type facial palsy, and dysarthria lasting between four and ten minutes. These episodes typically began while standing or eating and occurred one to three times daily. His neurologic examination was notable for a left hemiparesis (MRC grade 2 to 3), dysarthria, and left central type facial palsy; however, neglect and visual field defects were not observed. The patient was treated with intravenous heparin for six days during which period he continued to have TIAs. He was then switched to a combination of aspirin (325 mg daily)

and clopidogrel (75 mg daily after a loading dose of 225mg), but again continued to have TIAs. Blood pressure augmenting medications were not used.

On hospital day thirteen a cerebral angiogram was obtained which demonstrated moderate stenosis (>50%) of the right proximal MCA with decreased flow to the dominant lenticulostriate artery (Fig. 3A). Intracranial stenosis around the ostia of the dominant lenticulostriate artery in the right MCA was also observed. The right cerebral cortex was perfused antegrade by the right MCA without evidence of delayed filling (Fig. 4A). After intra-arterial injection of urokinase (100,000 units), the proximal MCA stenosis was treated with balloon angioplasty using a 2.0 × 20 mm coronary balloon without placement of a stent. This resulted in increased flow to the dominant lenticulostriate artery. Angioplasty resulted in a small intracranial dissection with thrombus visualized at the level of the dominant lenticulostriate artery (Fig. 3B) resulting in a narrowed lumen of the right MCA. Urokinase (200,000 units) and abciximab (4mg) were administered locally and intra-venous heparinization was initiated. Follow-up angiography four hours later revealed a MCA dissection with a thrombus; however, the size of thrombus had not changed. The patients did not have any additional TIAs following angioplasty.

The patient was seen in follow-up three months later, at which time he had not experienced any further neurological symptoms. A follow-up angiogram, obtained at this time, demonstrated preserved caliber of the dominant lenticulostriate artery and normal flow through this vessel. There was, however, interval narrowing of the right MCA at the site of the dissection (Fig. 3C) with resultant impairment of antegrade flow through this segment (Fig. 4B). SPECT, however, demonstrated improved perfusion to the right MCA cortex compared to the baseline SPECT suggesting that leptomeningeal collaterals had compensated for the worsening of the right MCA stenosis (Fig. 2C). SPECT also demonstrated slightly improved vascular reserve in the deep brain regions compared with the baseline study, likely as a result of improved flow through the dominant lenticulostriate (Fig. 2D).

Follow-up cerebral angiography after three years showed a near occlusion of the proximal right MCA. A network of perforating arteries which connected with the distal portion of the MCA had formed. This, together with leptomeningeal collaterals, and collaterals from the right posterior cerebral artery (PCA) and ACA supplied the right MCA territory (Fig. 3D, 4C). Thus, the patient did not have a successful long-term angiographic outcome from angioplasty.

Discussion

This case describes an unusual cause and an unusual course of a lacunar syndrome. Although the patient presented with lacunar-type TIAs, imaging studies showed the cause to be large artery stenosis. The “capsular warning syndrome” is generally thought to result from small vessel disease involving a dominant lenticulostriate artery. In this patient, however, the presumed cause is hemodynamic insufficiency in the perforator territory due to large artery atherosclerosis. Patient with the capsular warning syndrome have a very high risk of going on to infarction in the first ten days. Our case illustrates that transient symptoms can recur over the span of a month without becoming permanent and that angioplasty may cease the occurrence of the TIAs.

The term capsular warning syndrome was coined by Donnan et al[7] to describe a distinct type of transient ischemic attack (TIA) syndrome, consisting of repeated stereotyped bursts of unilateral motor and/or sensory deficits without cortical symptoms. Previous reports on “capsular warning syndrome” have focused on the clinical manifestations, location of

lesions, and epidemiologic characteristics and prognosis[7-15]. The syndrome is usually caused by in situ small penetrating vessel disease and treatment is typically limited to antithrombotic agents for prevention of further attacks. Even with antithrombotic therapy, this syndrome has a high probability of developing into a capsular stroke[7]. In Donnan's series of patients with "capsular warning syndrome" 40% (22 of 50 patients) developed a stroke within 10 days. Our case demonstrates that the capsular warning syndrome can be caused by atherosclerotic disease of the MCA involving the ostium of a dominant lenticulostriate artery and that angioplasty can be used successfully to abolish medically refractory TIAs.

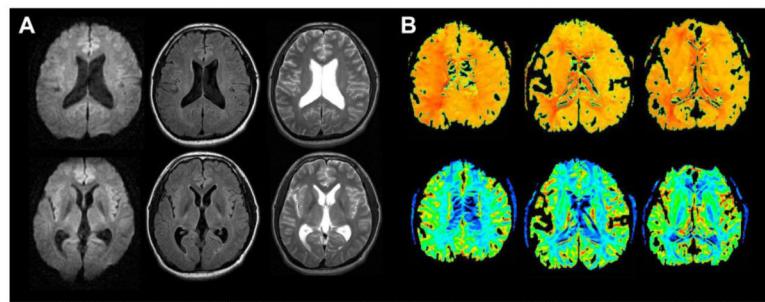
The capsular warning syndrome is caused by ischemia in the territory of a lenticulostriate artery. Most lenticulostriate arteries arise from the MCA, with typically 4-15 small arteries arising from each MCA. Occasionally at lenticulostriate arteries, arteries arise from a single trunk[16]. Our patient had such a single dominant lenticulostriate artery. We speculate that patients with a single lenticulostriate trunk are at increased risk of developing the capsular warning syndrome due to relatively poor collateralization of the lenticulostriate territory. Small vessel disease is believed to be the most common cause of hemodynamic compromise in the lenticulostriate territory. Various other mechanisms have also been suggested, including artery to artery emboli, vasospasm, peri-infarct depolarization, and, in rare instances, atherosclerotic disease of the MCA[17]. In Donnan's series of 50 patients with "capsular warning syndrome", 27 patients underwent angiography and only one patient exhibited high-grade stenosis of the ipsilateral MCA[7]. Our patient's proximal MCA stenosis involved the orifice of a dominant perforating artery causing hemodynamic insufficiency of the lenticulostriate artery territory. This was evidenced by the patient's symptoms and by the findings on brain SPECT. The latter demonstrated decreased vascular reserve of the deep brain structures consistent with hemodynamic impairment in the territory of the dominant lenticulostriate artery secondary to MCA stenosis.

Antiplatelets, heparin, pressors and thrombolytics have all been used to treat patients with capsular warning syndrome[11,18]. It remains uncertain if any of these therapies alter the natural history of this syndrome. Intracranial angioplasty has, to our knowledge, not previously been reported as a treatment for the capsular warning syndrome. Indeed, angioplasty and stenting of the MCA is associated with a risk of lenticulostriate ischemia thought to result from perforator obstruction by displacement of atheroma[19]. The risk of perforator obstruction is particularly high in patients with pre-procedural infarction in their perforator territory. Eight percent of these patients have been reported to develop a procedural infarct compared to less than one percent of patients who do not have a pre-procedural lenticulostriate infarct. Prior to angioplasty, our patient continued to have TIAs despite antiplatelet and anticoagulation therapy. Intracranial angioplasty resulted in improved flow to the dominant lenticulostriate and resolution of the patient's TIAs. Intracranial angioplasty can lead to various complications including vessel dissection, vessel rupture, arterial thrombosis, distal embolization, and perforator stroke. Our patient developed an MCA dissection during angioplasty. Although not flow limiting at first, at 3 year follow-up the MCA was occluded just distal to the lenticulostriate trunk. This may have been due to progression of the dissection or progressive atherosclerosis. Fortunately this did not cause a stroke as flow was maintained to dominant lenticulostriate and the patient had good cortical collaterals.

In summary, this case demonstrates that the capsular warning syndrome can be caused by atherosclerotic disease of the MCA involving the ostium of a single lenticulostriate trunk and that angioplasty can be considered as a potential intervention in this setting for patients who fail medical therapy.

References

- [1]. Easton JD, Saver JL, Albers GW, Alberts MJ, Chaturvedi S, Feldmann E, et al. Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists. *Stroke*. 2009; 40:2276–93. [PubMed: 19423857]
- [2]. Purroy F, Montaner J, Molina CA, Delgado P, Ribo M, Alvarez-Sabin J. Patterns and predictors of early risk of recurrence after transient ischemic attack with respect to etiologic subtypes. *Stroke*. 2007; 38:3225–9. [PubMed: 17962602]
- [3]. Lisabeth LD, Ireland JK, Risser JM, Brown DL, Smith MA, Garcia NM, et al. Stroke risk after transient ischemic attack in a population-based setting. *Stroke*. 2004; 35:1842–6. [PubMed: 15192239]
- [4]. Hill MD, Yiannakoulias N, Jeerakathil T, Tu JV, Svenson LW, Schopflocher DP. The high risk of stroke immediately after transient ischemic attack: a population-based study. *Neurology*. 2004; 62:2015–20. [PubMed: 15184607]
- [5]. Kleindorfer D, Panagos P, Pancioli A, Khouri J, Kissela B, Woo D, et al. Incidence and short-term prognosis of transient ischemic attack in a population-based study. *Stroke*. 2005; 36:720–3. [PubMed: 15731465]
- [6]. Donnan GA, O'Malley HM, Quang L, Hurley S. The capsular warning syndrome: The high risk of early stroke. *Cerebrovasc Dis*. 1996;202–7.
- [7]. Donnan GA, O'Malley HM, Quang L, Hurley S, Bladin PF. The capsular warning syndrome: pathogenesis and clinical features. *Neurology*. 1993; 43:957–62. [PubMed: 8492952]
- [8]. Tang CW, Wang PN, Lin KP, Huang DF, Wang SJ, Chen WT. Microscopic polyangiitis presenting with capsular warning syndrome and subsequent stroke. *J Neurol Sci*. 2009; 277:174–5. [PubMed: 19033078]
- [9]. Caporale CM, Notturno F, Caulo M, Uncini A. Capsular warning syndrome mimicking a jacksonian sensory march. *J Neurol Sci*. 2009; 285:262–4. [PubMed: 19664779]
- [10]. Teng HW, Hong CT. Capsular warning syndrome: report of a case. *Acta Neurol Taiwan*. 2008; 17:248–52. [PubMed: 19280869]
- [11]. Saposnik G, de Tilly L, Noel, Caplan LR. Pontine warning syndrome. *Arch Neurol*. 2008; 65:1375–7. [PubMed: 18852355]
- [12]. Staaf G, Geijer B, Lindgren A, Norrving B. Diffusion-weighted MRI findings in patients with capsular warning syndrome. *Cerebrovasc Dis*. 2004; 17:1–8. [PubMed: 14530631]
- [13]. Oliveira-Filho J, Ay H, Koroshetz WJ, Buonanno FS. Localization of clinical syndromes using DWI: two examples of the “capsular” warning syndrome. *J Neuroimaging*. 2001; 11:44–7. [PubMed: 11198526]
- [14]. Ferro JM, Falcao F, Melo TP, Campos JG. Dural sinus thrombosis mimicking “capsular warning syndrome”. *J Neurol*. 2000; 247:802–3. [PubMed: 11127538]
- [15]. Farrar J, Donnan GA. Capsular warning syndrome preceding pontine infarction. *Stroke*. 1993; 24:762. [PubMed: 8488536]
- [16]. Aydin IH, Takci E, Kadioglu HH, Kayaoglu CR, Tuzun Y. The variations of lenticulostriate arteries in the middle cerebral artery aneurysms. *Acta Neurochir (Wien)*. 1996; 138:555–9. [PubMed: 8800331]
- [17]. Herve D, Gautier-Bertrand M, Labreuche J, Amarenco P. Predictive values of lacunar transient ischemic attacks. *Stroke*. 2004; 35:1430–5. [PubMed: 15118181]
- [18]. Vivanco-Hidalgo RM, Rodriguez-Campello A, Ois A, Cucurella G, Pont-Sunyer C, Gomis M, et al. Thrombolysis in capsular warning syndrome. *Cerebrovasc Dis*. 2008; 25:508–10. [PubMed: 18477844]
- [19]. Levy EI, Chaturvedi S. Perforator stroke following intracranial stenting: a sacrifice for the greater good? *Neurology*. 2006; 66:1803–4. [PubMed: 16801640]

**Fig. 1.**

Initial brain MRI does not show acute infarction; however, an old small deep infarction is seen in the right periventricular area (A). Time-to-peak map indicates a mildly delayed perfusion in the right middle cerebral artery territory (B, upper), but no significant perfusion impairment is observed in the corresponding region on the cerebral blood volume map (B, bottom).

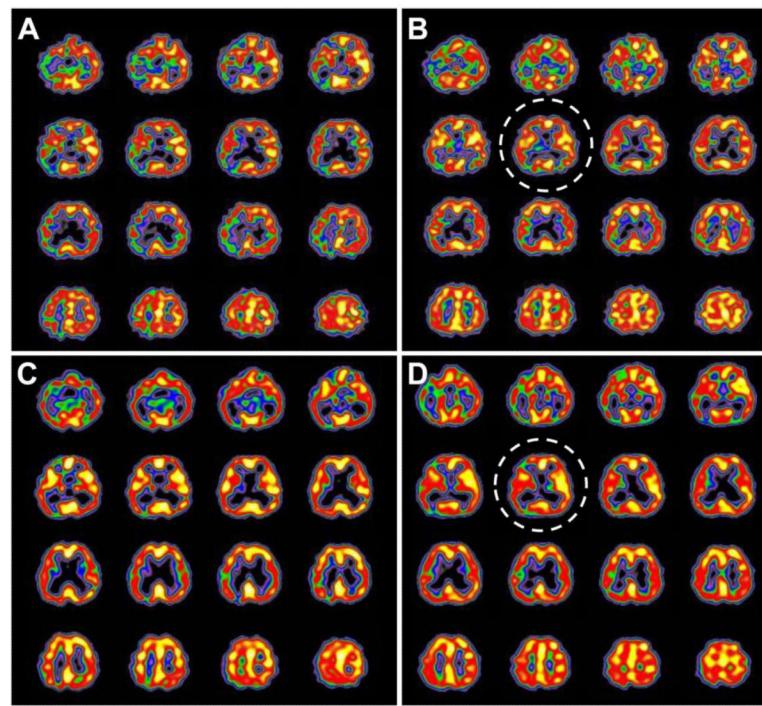
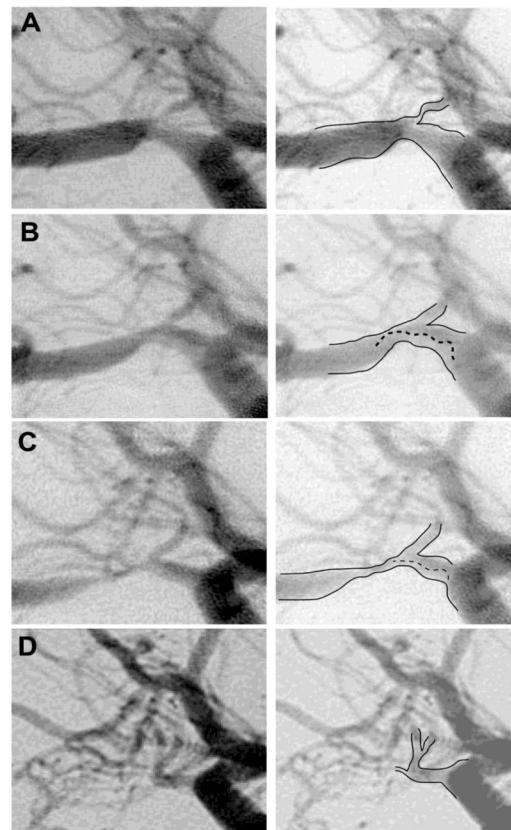
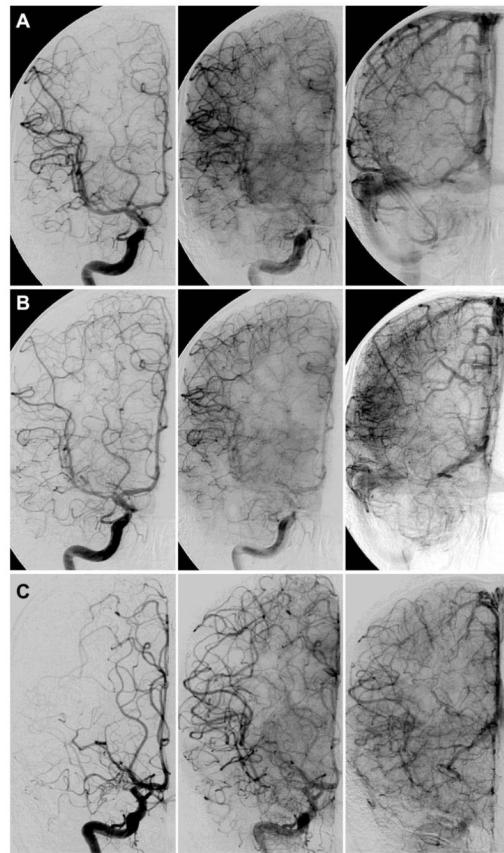


Fig. 2.

Pre-procedural brain single photon emission computed tomography (SPECT) and follow-up SPECT performed three months after angioplasty. Initial pre-procedural brain SPECT was performed five days after admission. Initial basal brain SPECT reveals impaired perfusion in the right MCA territory including the cortex and deep hemisphere (A); however, perfusion is relatively conserved in the cortex, which is supplied by middle cerebral artery (MCA). Impaired vascular reserve is seen in the deep hemisphere (interrupted circle) after injection of acetazolamide (B). Follow-up basal brain SPECT (C) indicates mildly decreased perfusion in the right MCA; however, these findings are improved as compared with those of the previous study. No significant perfusion defect is observed in the cortex and deep hemisphere after injection of the acetazolamide. Vascular reserve after injection of the acetazolamide in the deep brain region (interrupted circle) in (D) is improved compared with the previous study.

**Fig. 3.**

Transfemoral cerebral angiography examinations were performed at separate intervals (A, pre-procedure; B, four hours after angioplasty; C, three months after angioplasty; D, three years after angioplasty). The presumed inner margin of the lumen in the right MCA and proximal portion of the right dominant lenticulostriate artery are shown in the right side of each figure. Pre-procedural cerebral angiography reveals right middle cerebral artery (MCA) stenosis with decreased flow to the dominant lenticulostriate artery (A). A post-angioplasty follow-up image shows the dissecting flap (dotted line) and thrombus; however, flow to the dominant lenticulostriate artery is improved compared with the previous study (B). Right MCA stenosis progresses with conserved flow to the dominant right MCA (C). The proximal portion, post-ostia of the lenticulostriate artery, of the right MCA is nearly occluded with the collateral basal small arteries forming a complex connecting to the distal portions of the MCA; however, flow to the dominant lenticulostriate artery is conserved (D).

**Fig. 4.**

Transfemoral cerebral angiography examinations were performed at separate intervals (A, pre-procedure; B, three months after angioplasty; C, three years after angioplasty). These images reveal arterial filling status and delayed perfusion. No significant regions which show filling defects during the capillary phase, are seen on the pre-procedural cerebral angiography (A). Cerebral angiography reveals significant stenosis of the right MCA and relatively conserved cortical arterial filling three months after angioplasty (B). Delayed perfusion and impaired perfusion areas with occlusion of the proximal MCA and small collateral vascular networks between perforating arteries are seen three years after angioplasty (C).