4 脳神経外科手術
—JET, MELT Japan など—

はじめに

近年では，脳神経外科領域においても，内頸動脈狭窄症に対する外科的治療と，内科的治療の大規模ランダム化比較試験や頭蓋外内血行再建術の有効性に関する大規模ランダム化比較試験の報告がなされている．本稿では，わが国で実施された，または進行中の大規模ランダム化比較試験として，Japanese EC-IC Bypass Trial(JET Study)とMCA-Embolism Local Fibrinolytic Intervention Trial Japan(MELT Japan)に関して述べる．

1 JET Study

頭蓋外—頭蓋内(EC-IC)バイパス術の有効性を証明すべく，1977～82年に世界的規模で大規模ランダム化比較試験が行われた．しかしその結果は，EC-ICバイパス術には内科的治療に優る脳梗塞再発予防効果はないとするものであった[1]．この研究結果の最も大きな欠点は，患者選択に際し貧困灌流症候群の概念が導入されていないことにあった．そこで貧困灌流の存在する症例のみを集めて検討を行えばバイパス術の有効性を証明できるのではないかと考えられ，JET Studyが開始された．本研究の特徴は以下の3点である．

①脳循環の測定を定量的に行い，貧困灌流を有する患者のみを対象とする．

②対象を薬物療法のみの群あるいは薬物療法+EC-ICバイパス術の群のいずれかにランダムに割り付け，2

年間追跡し，脳梗塞再発作の頻度を比較する．

③両群間で高次脳機能の改善・悪化についても比較し，慢性虚血による高次脳機能障害に対するEC-ICバイパス術の有効性についても検討する．

本研究は1998年に開始され，2004年3月で経過観察期間を終了した．対象症例は，内頸動脈系の閉塞性脳血管病変による一過性脳虚血発作または完成卒中を3カ月以内に認めた症例で，以下のinclusion criteriaを満たすものである．

①73歳以下でADLがほぼ自立している(modified Rankin Scale；mRS 1,2)．

②CTないしはMRIにて一血管支配領域にわたる広範な脳梗塞巣を認めない．

③血管撮影上内頸動脈，中大脳動脈本幹の閉塞あるいは高度狭窄(内頸動脈内膜剝離術の対象となる内頸動脈狭窄を除く)がある．

④3次元的定量的脳血流測定法にて，病側中大脳動脈灌流域の安静時血流量が正常値の80％未満，かつアセタゾラミド反応性が10％未満であること．

高次脳機能障害に対するEC-ICバイパス術の有効性に関しては，いまだ最終報告がなされていないが，脳卒中再発率に関しては外科的治療群が内科的治療群に比べ有意に低いことが示された．さらに全死亡に関しても，外科的治療群のほうが有意に内科的治療群より少なかった．また，JET Studyの脳循環criteria内ではその重症度と再発頻度には相関がなく，より緩やかなcriteriaでも外科的治療の有効性が存在することが示唆されている．

貧困灌流を有する症例においてはEC-ICバイパス術の脳卒中予防効果が証明されたといえる．

2 MELT Japan

脳梗塞急性期に t-PA 静脈投与を行うことにより，患者転帰が改善することが大規模ランダム化比較試験にて示されている．わが国においても，2005 年 10 月に経静脈的投与に対して薬事認可された．しかし局所線溶療法に関しては，その有効性は十分検討されていない．

超急性期局所線溶療法多施設共同試験 MELT Japan はウロキナーゼを用い，超急性期局所線溶療法の有効性を評価することを目的に 2001 年より開始された．対象は急性中大脳動脈閉塞による虚血性脳血管障害患者とした．選択基準は下記の通りである．

①血管撮影で急性中大脳動脈閉塞が確認された患者，
②発症時刻が特定可能で発症後 6 時間以内に局所線溶療法が開始できる患者，
③入院直後の CT でまったく変化を認めないか，病側に軽微な初期虚血変化のみを認めるもの，
④ CT 撮像後より 2 時間以内に局所線溶療法を開始できる患者，
⑤年齢 20 歳以上 75 歳以下．

局所線溶療法群はウロキナーゼ動注を行い，対照群は局所線溶療法(動注，静注どちらも)以外の一般的治療を行うこととした．エンドポイントは発症 3 カ月での mRS を比較することとした．

目標症例数は 200 例であるが，2005 年 10 月時点で 115 例が登録されている．研究終了予定は 2007 年 3 月である．3 カ月経過観察を終了した 105 例に対して，中間解析が施行された．その結果は，死亡および神経学的増悪を伴う脳内出血発生頻度において 2 群間に有意差は認めなかった．有効性に関しては，mRS 2 以下(家庭内自立)となった頻度はウロキナーゼ群 49.1 %，対照群 38.5 %とほぼ同等であったが，mRS 1 以下(社会復帰率)はウロキナーゼ群

41.5％，対照群21.2％とウロキナーゼ群に有意に多かった（$P=0.035$）。

急性期中大脳動脈閉塞症例に局所線溶療法を行うことは社会復帰率を改善する可能性があると考えられる。

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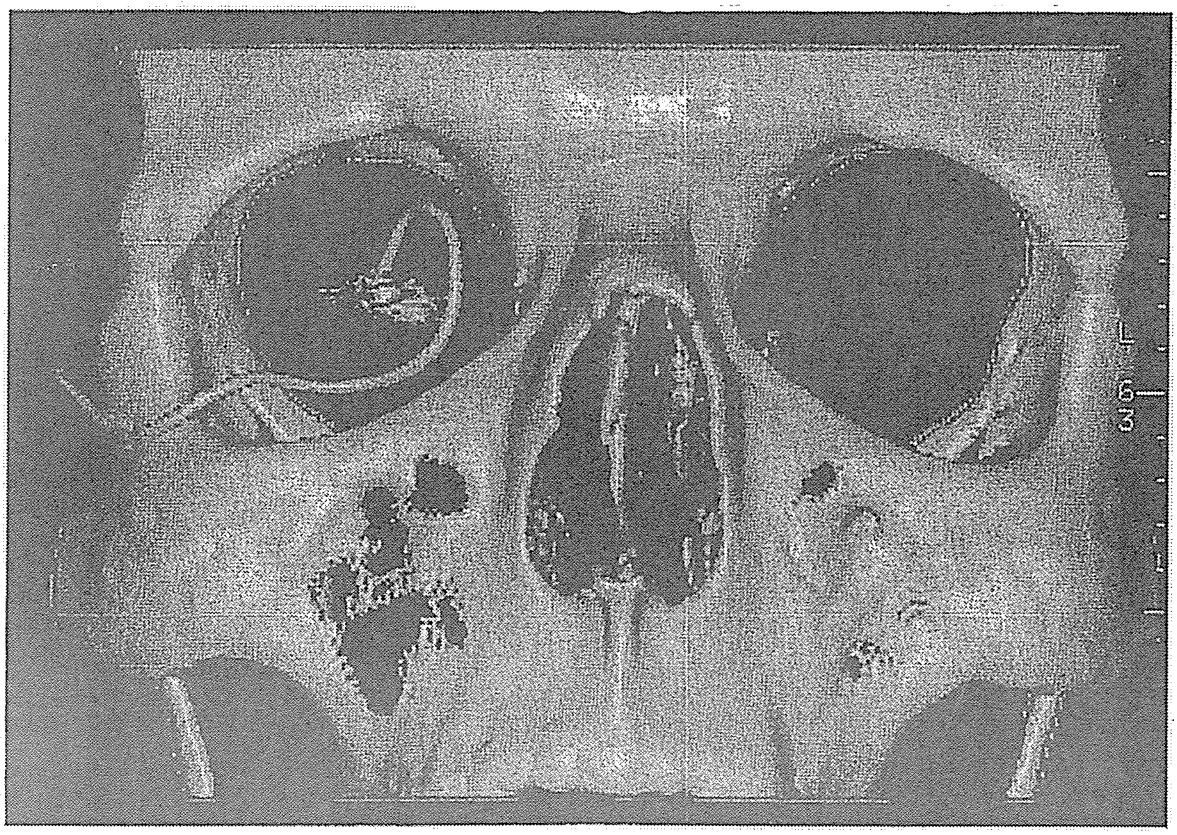

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Introduction: The aim of this study was to evaluate the cognitive performance and the functional results in patients with AcoA aneurysms treated by different options such as microsurgical clipping (MC) and endovascular coiling (EC).

Methods: Between 2002 and 2004, 53 consecutive patients treated for a AcoA bleeding with a Glasgow Outcome Score of 4 or 5 (MC, n = 39 ; EC, n = 14) were prospectively selected in order to perform a neuropsychological and functional evaluation at 6 months. All patients were tested during a 3 h extensive neuropsychological battery of tests during 2 sessions (the patient alone and with a close relative). Statistical anlysis: t test, Mann Whitney Test.

Results: Any significant differences between the MC group and the EC was primarily found in global efficiency, memory tests [Badeley Doors test, Rey Complex Figure test, Gröber and Buschke tests] (pathologic in 51.3% vs 42.8% respectively) and executive test [Trail making test, Stroop test, Wisconsin Card sorting test, Verbal fluency and Brixton test](20.5% vs 28.5%). Surgically treated patients showed a significant impairment in their anosognosic symptoms (25.6% vs 0%, $p = 0.019$). Functional results were similar in both groups: RNLI (20.5% vs 14.3%, NS), modification of professional status (20,5% vs 14,3%, NS) and modified Rankin Score (0: 28.1% vs 28,6%, 1: 45,2% vs 14.3%, 2: 17.9% vs 50, 3: 7.7% vs 7.4%; NS).

Conclusions: Investigation of neuropsychological deficits showed impairment even in patients classified with a favorable outcome but no significant difference was observed as regards surgical or endovascular treatment.

PAPER 644

Effect of STA-MCA Bypass for the Ocular Ischemic Syndrome due to the Occlusive Internal Carotid Artery Diseases

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Introduction: The authors examined the role of the STA-MCA bypass for chronic ocular ischemic syndrome (OIC) due to the occlusive internal carotid artery (ICA) diseases.

Methods: We examined the visual symptoms and the ophthalmic artery flow using color Doppler flow imaging (CDFI) in forty-four patients having the chronic OIS due to the occlusive ICA diseases treated with STA-MCA bypass. Visual symptoms were decline of visual acuity in 31 cases, frequent amaurosis fugax in 6 cases and both in 7 cases.

Results: 1. CDFI findings: 1) Preoperatively, 39 patients showed reversed ophthalmic artery flow (mean PFV: −0.32 m/sec). The other 5 patients showed antegrade ophthalmic artery flow (mean PFV: 0.09 m/sec). 2) At one month after bypass, 17 patients showed the antegrade ophthalmic artery flow. Mean PFV in the patients with preoperatively reversed ophthalmic artery flow significantly rose to −0.07 m/sec ($p < 0.05$). 3) At three months after surgery, 21 patients showed the antegrade flow. Mean PFV in the patients with preoperatively reversed ophthalmic artery flow significantly increased to 0.08 m/sec ($p < 0.05$). There was no significant change of CDF finding in patients with preoperative antegrade ophthalmic artery flow. 2. Visual symptoms: During the follow-up period (mean 4.9 years), visual acuity improved in 18 patients (47%) and did not worsen in any of the remaining 26 patients.

Conclusions: STA-MCA bypass was useful and important role for the improvement or prevention of progress of the OIS due to the occlusive ICA diseases, especially for the patients showing the reversed ophthalmic artery flow.

PAPER 645

Multimodality Management of 81 Pediatric Arteriovenous Malformations

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Introduction: Arteriovenous malformations are considered to be congenital in origin, though recent reports challenge the uniformity of this statement. Children make up between 3 and 20% of the patients with AVMs in the literature, however, AVMs are responsible for 30 to 50% of intracranial hemorrhages in children.

Methods: Between 1983 and 2005, 87 children (age 18 or under) were treated at St. Joseph's Hospital and Medical Center for intracranial arteriovenous malformations. The inpatient and outpatient charts of 81 patients were available for retrospective review.

Results: The majority of patients (48) 59% presented with hemorrhage. Another 17% presented with seizures, and 12% were found incidentally. Patients with brainstem lesions presented at a significantly younger age ($p = 0.0015$) than any other location. Lesions in the frontal lobes were significantly smaller than other locations, and thalamic lesions significantly larger ($p = 0.01$ and 0.005) Recurrences occured more frequently in the first 12 years than in the latter 12. Most patients with smaller lesions (grades I to III) underwent craniotomy alone, whereas nearly all patients with grade IV and V lesions underwent embolization, craniotomy and radiosurgery. Outcome was better for patients with grade I lesions than any other grade. Patients presenting with hemorrhage had a worse outcome than other presentations.

Conclusions: Children appear to be more prone to recurrence than adults with AVMs. The combination of endovascular, open surgical and radiosurgical techniques offers the best opportunity for cure with the lowest side effects. Long term follow-up is essential in all patients.

PAPER 646

Treatment of Traumatic Brain Injury in Rats with a Combination Therapy of Marrow Stromal Cells and Atorvastatin

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Introduction: This study investigated the effects of combination therapy of marrow stromal cells (MSCs) and statins (atorvastatin) after traumatic brain injury (TBI) in rats.

Methods: 36 adult female Wistar rats were injured with controlled cortical impact and divided into four equal groups. Group I was injected with MSCs (1×10^6) intravenously 24 hrs after TBI. Group II was administered atorvastatin (0.5 mg/kg) orally for 14 days starting 24 hrs after TBI. Group III received MSCs (1×10^6) combined with atorvastatin (0.5 mg/kg), whereas Group IV (control) was injected with saline. MSCs were harvested from bone marrow of male Wistar rats in order to identify male donor cells within female recipient animals by localizing Y chromosomes within them. Functional analysis was performed using modified neurological severity scores and Morris Water Maze test. Animals were killed 35 days after injury and brain sections stained with immunohistochemistry.

Results: There was no improvement in functional outcome in animals treated with MSCs or atorvastatin alone (Groups I & II). However, in animals receiving combination therapy (Group III) significant functional improvement was seen with both testing modalities. Microscopic analysis showed that significantly more MSCs were present in animals receiving combination therapy than those receiving MSCs alone. Also, there was significant endogenous cellular

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Effect of Carotid Artery Stenting on Ocular Circulation and Chronic Ocular Ischemic Syndrome

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Key Words

Carotid artery stenting · Chronic ocular ischemic syndrome · Color Doppler flow imaging · Ophthalmic artery flow

Abstract

Background: The authors evaluated the effect of carotid artery stenting (CAS) on ocular circulation and chronic ocular ischemic syndrome. ***Methods:*** We examined 38 patients with carotid artery stenosis (>80%) at its origin treated with CAS. Ocular circulation and symptoms were examined before, within 24 h, and 1 week, 1 month, and 3 months after CAS based on ophthalmic artery color Doppler flow imaging and ophthalmological examinations. ***Results:*** Ocular circulation: Before CAS, 13 patients showed reversed ophthalmic artery flow, and 25 antegrade flow. Average peak systolic flow velocity was –0.038 m/s. Within 24 h after CAS, all patients showed antegrade ophthalmic artery flow; reversed flow before CAS was thus resolved. Average peak systolic flow velocity rose significantly to 0.36 m/s ($p < 0.05$). One week, 1 month and 3 months after CAS, there were no significant changes compared to the findings at 1 week after CAS. Ocular symptoms: Before CAS, 8 patients showed chronic ocular ischemic syndrome. During the follow-up period (mean: 2.8 years), the visual acuity improved in 7 cases. Average retinal artery pressure and arm-to-retina circulation time improved significantly to the normal level ($p < 0.05$). The other 30 patients complained of recurrent and worsened visual symptoms during the follow-up period. ***Conclusion:*** CAS was effective in improving ocular circulation, and also improved the chronic ocular ischemic syndrome caused by the severe carotid artery stenosis.

Introduction

The efficacy and safety of carotid endarterectomy for internal carotid artery stenosis at its origin has been confirmed previously by various prospective, randomized, and multicentered studies [1–4]. Recently, carotid angioplasty with stent placement has emerged as a potential safe and effective alternative to carotid endarterectomy [5–8]. Carotid artery stenting (CAS) can restore the cerebral perfusion pressure and improve the hemodynamic status of the brain [6, 9, 10]. One of the important clinical aspects of internal carotid artery stenosis at its origin is its influence on the flow dynamics of the ophthalmic artery. The disturbed ophthalmic artery flow correlates with the chronic ocular ischemic syndrome symptoms such as amaurosis fugax or a decline of visual acuity [11, 12]. Therefore, it is important to understand the ophthalmic artery flow and ocular symptoms in patients with internal carotid artery stenosis before and after CAS.

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In this study, the authors discussed and analyzed the effect of CAS on ocular circulation and chronic ocular symptoms in the patients with severe carotid artery stenosis.

Patients and Methods

Patients

From January 2002 to March 2005, the authors examined ophthalmic artery color Doppler flow imaging (CDFI) in 38 consecutive patients with internal carotid artery origin stenosis (>80%) treated with CAS. Thirty-two patients were male and 6 female. Ages ranged from 47 to 79 years, with a mean of 70 years. The clinical symptoms of the patients were transient ischemic attack in 29, and reversible ischemic neurological deficit in 9. According to the criteria of the NASCET study [4], the grades of angiographical internal carotid artery stenosis on the ipsilateral side were greater than 95% in 9 patients, 90% in 16 patients, and 80% in 13 patients. Stenosis of the ipsilateral external carotid artery at its origin was evaluated in each patient. Four patients had 30–50% stenosis, 9 patients had less than 30% stenosis, and the 25 patients did not show any apparent stenosis. The contralateral internal carotid artery was also evaluated. There was occlusion in 8 patients, 50–80% stenosis in 3 patients, less than 50% stenosis in 12 patients and no apparent stenosis in 15 patients.

Eight patients complained of chronic ocular ischemic syndrome. All 8 had a visual acuity of 20/40 or worse, and 2 had frequent amaurosis fugax. In these 8 patients, tiny or no iris rubeosis was seen, and intraocular pressure was normal (less than 25 mm Hg). No patients showed blindness. The exclusion criteria for chronic ocular ischemic syndrome were acute ocular ischemic symptoms such as sudden loss of vision, a single episode of amaurosis fugax, or ocular/orbital pain [13].

CAS was performed at least 4 weeks after the last attack for each patient using a smart stent. At the end of the procedure, the patency of the treated carotid artery lumen was confirmed in each case by angiography. No patient complained of permanent periprocedure neurological deficit due to the CAS procedure.

All patients were followed up for clinical symptoms after CAS. The follow-up period was 0.9 to 4.5 years (mean: 2.8 years). During this period, none of the patients had a recurrent neurological ischemic attack or worsening of the symptoms including ocular signs. At the final stage, no patients showed any neurological deficit.

Methods

To evaluate ocular circulation, the authors examined ophthalmic artery flow by color Doppler flow imaging (CDFI) with Computed Sonography 128XP/10 (Acuson Corp., Mountain View, Calif., USA). With a 5-MHz probe, the power was less than 50 mW/cm^2, and the examination was completed within 5 min in each eye. The ophthalmic artery CDFI findings from the ipsilateral side of CAS were analyzed. Ophthalmic artery CDFI was performed within 1 week before CAS, within 24 h (mean: 7.6 h), and 1 week, 1 month, and 3 months after CAS in each patient. These CDFI studies provided information regarding flow direction and peak systolic flow velocity of the ophthalmic artery.

The authors also performed ophthalmic artery CDFI on 36 normal healthy volunteers. Ages ranged from 37 years to 73 years, and the mean age was 62 years. 19 volunteers were male and 17 female. All volunteers showed normal flow direction, i.e. flow away from the orbital apex to the globe. Average peak systolic flow velocity was 0.36 ± 0.07 m/s.

All patients were examined for ocular symptoms such as visual acuity and amaurosis fugax before the CAS procedure and during the follow-up period. In patients showing chronic ocular ischemic syndrome before CAS, retinal artery pressure and arm-to-retina circulation time were also examined using fluorescent angiography before and after CAS.

The physiological data were compared using two-tailed paired or unpaired Student's t test, simple regression analysis, ANOVA and χ^2 test. $p < 0.05$ was considered as a threshold for statistical significance. All values are reported as means ± standard deviation (SD).

Results

Ophthalmic Artery Color Doppler Flow Imaging

Before CAS

The ophthalmic artery flow was reversed in 13 patients and antegrade in 25 patients. Peak systolic flow velocities ranged from –1.63 to 0.54 m/s, with an average of –0.038 ± 0.47 m/s. Average peak systolic flow velocity in the patients with reversed flow was –0.57 ± 0.40 m/s, and in those with antegrade flow 0.24 ± 0.12 m/s. The average stenosis of the internal carotid artery was 87.0 ± 5.16% in the patients with antegrade flow, and 95.3 ± 2.10% in those with reversed flow. There was a significant difference between these two stenosis values ($p < 0.00001$) using two-tailed unpaired t test.

The relationship between the degree of internal carotid artery stenosis and peak systolic flow velocity of the ophthalmic artery was examined. There was a statistically significant negative correlation using simple regression analysis ($p = 0.0002$) (fig. 1a). To evaluate the effect of the contralateral internal carotid artery stenosis, the 38 patients were divided into two groups according to the degree of stenosis. Group A consisted of 11 patients with more than 50% stenosis. Group B consisted of 27 patients with less than 50% or no apparent stenosis . In each group (fig. 1b, c) there was a statistically significant negative correlation between the degree of the internal carotid artery stenosis and ophthalmic artery peak systolic flow velocity on simple regression analysis ($p = 0.02$ in group A, $p = 0.0002$ in group B). Moreover, there was a significant difference between these two regression lines in groups A and B using ANOVA ($p = 0.0002$).

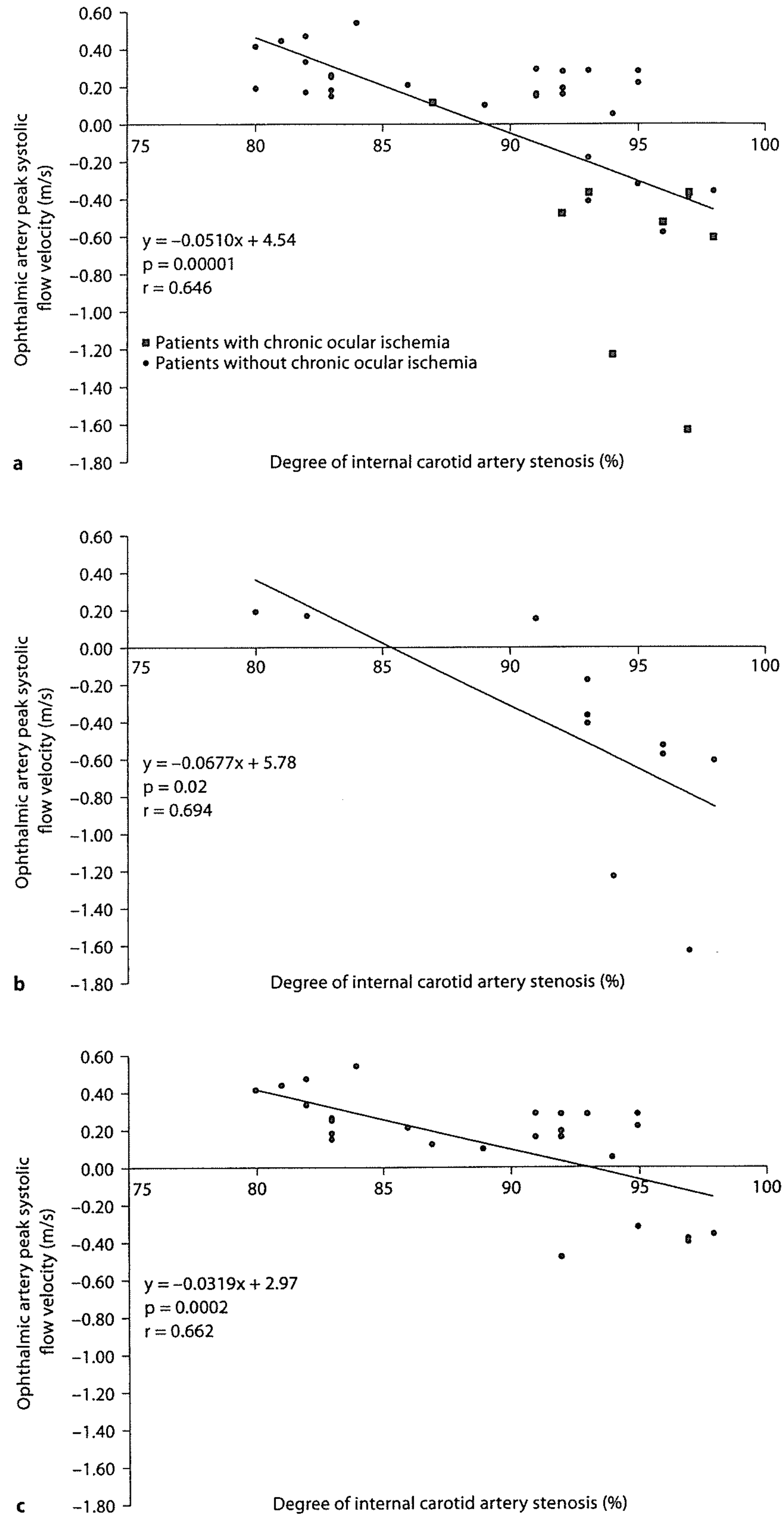


Fig. 1. Graphs showing the correlation between the degrees of internal carotid artery stenosis and the ophthalmic artery peak systolic flow velocities in all 38 patients (**a**), in group A consisting of 11 patients with contralateral internal carotid artery occlusion or more than 50% stenosis (**b**), and in group B consisting of 27 patients with less than 50% or no contralateral internal carotid artery stenosis (**c**).

Within 24 h after CAS

The patients showing reversed ophthalmic artery flow before CAS all returned to the normal antegrade flow following CAS. Peak systolic flow velocities ranged from 0.16 to 0.64 m/s. The overall average flow velocity rose to 0.36 ± 0.13 m/s, which is statistically significant compared with the level before CAS using two-tailed paired t test (p = 0.00002). Moreover, average peak systolic flow velocity did not significantly differ from that of controls on two-tailed unpaired t test.

One Week after CAS

In all patients, flow in the ophthalmic artery was antegrade. The peak systolic flow velocities ranged from 0.15 to 0.57 m/s. The overall average flow velocity was 0.35 ± 0.12 m/s, but this was not significantly different from the value obtained within 24 h after CAS using two-tailed paired t test.

One Month after CAS

In all patients, flow in the ophthalmic artery was antegrade. The peak systolic flow velocities ranged from 0.13 to 0.58 m/s. The overall average flow velocity was 0.35 ± 0.12 m/s. This was not significantly different from the value at 1 week after CAS using two-tailed paired t test.

Three Months after CAS

In all patients, flow in the ophthalmic artery was antegrade. The peak systolic flow velocities ranged from 0.15 to 0.58 m/s. The overall average flow velocity was 0.35 ± 0.11 m/s. This was not significantly different from the value at 1 month after CAS using two tailed-paired t test.

Ocular Symptoms

Before CAS

Eight patients complained of chronic ocular ischemic syndrome. These 8 patients were given careful ophthalmological examinations before and after CAS. Of these 8 patients, 6 showed reversed ophthalmic artery flow, and 2 antegrade flow. The relationship between the chronic ocular ischemic syndrome and the reversed ophthalmic artery flow was significant using the χ^2 test (p = 0.006). Ischemic changes of the optic fundi in the 8 patients were neovascularization on the disc in 5 patients (63%), cotton wool patches in 3 (38%), and peripheral hemorrhage in 2 (25%). Average arm-to-retina circulation time was 54.6 ± 12.3 s, and average retinal artery pressure was 39.6 ± 8.00 mm Hg.

Three Months after CAS

Seven of eight patients with the chronic ocular ischemic syndrome before CAS showed improvement in visual acuity, but one showed no improvement despite the normal ophthalmic flow after CAS. Six patients had a visual acuity between 20/40 and 20/20, and 2 a visual acuity less than or equal to 20/40.

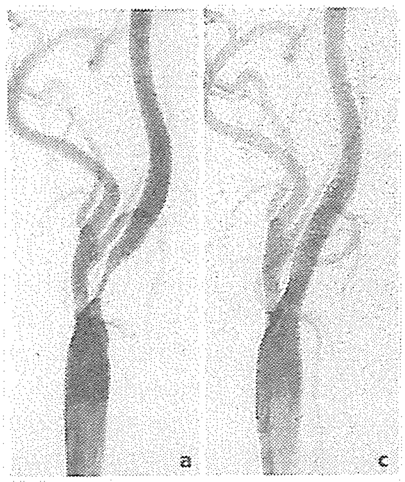
Final Stage (Mean 2.8 Years after CAS)

Of the 8 patients, 6 had visual acuities between 20/40 and 20/20, and 2 had visual acuities less than or equal to 20/40. Ischemic changes of the optic fundi seen before CAS were improved during the follow-up period. Examination of the optic fundi showed neovascularization of the disc in 1 case (13%), whereas the remaining 7 cases (87%) were normal. The average arm-to-retina circulation time dropped to 16.3 ± 2.82 s, which was significant on two-tailed paired t test (p = 0.004), and the average retinal artery pressure increased to 54.6 ± 12.3 mm Hg, which was also significant on two-tailed paired t test (p = 0.001).

Thirty patients showed no chronic ocular ischemic syndrome before CAS. During follow-up, these 30 patients complained of no chronic ocular ischemic syndrome such as disturbance of the visual acuity or frequent amaurosis fugax. CAS could prevent the presentation of the chronic ocular ischemic syndrome due to the severe carotid artery stenosis in these patients.

Illustrative Cases

A 73-year-old man was referred to the authors' hospital complaining of transient left hemiparesis and right visual acuity decline (20/160). The right retinal artery pressure was 43 mm Hg, and right arm-to-retina circulation time was 25 s. The optic fundi on the right side showed tiny neovascularizations on the disc and cotton wool patches. Right carotid angiography showed 98% stenosis of the right internal carotid artery at its origin (fig. 2a). The right ophthalmic artery CDFI showed reversed flow, and the peak systolic flow velocity was -0.36 m/s (fig. 2b). Right CAS was performed. At the end of the procedure, dilatation of the stenosis and stenting were confirmed on right carotid angiography (fig. 2c). Within 24 h after CAS, the right ophthalmic artery CDFI showed resolution of the reversed flow, and the peak flow velocity was 0.44 m/s (fig. 2d). The peak systolic flow velocity of the ophthalmic artery was 0.42 m/s at 1 week after CAS (fig. 2e), 0.41 m/s at 1 month after CAS (fig. 2f), and 0.43 m/s at 3 months after CAS (fig. 2g). Three months after CAS, right visual acuity gradually improved to 20/40,



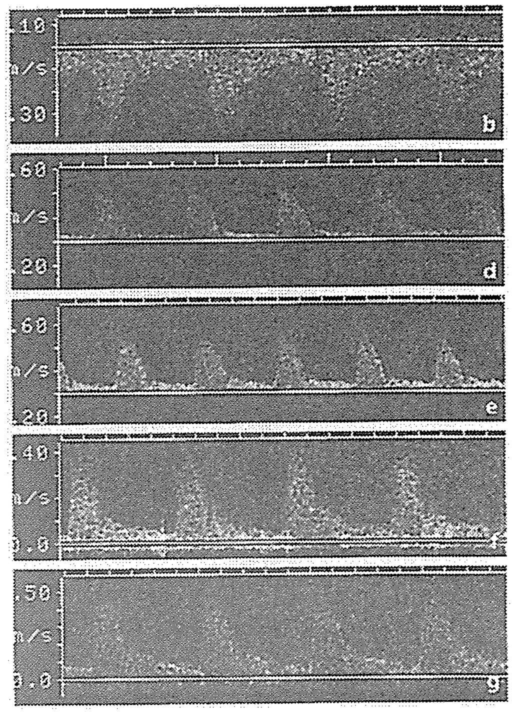


Fig. 2. a Before carotid artery stenting (CAS), right carotid angiography showing severe stenosis of the right internal carotid artery at its origin. **b** Before CAS, right ophthalmic artery color Doppler flow imaging (CDFI) showing the reversed ophthalmic artery flow direction. **c** After CAS, right carotid angiography showing the good patency of the CAS. **d** Right ophthalmic artery CDFI within 24 h after CAS showing the restoration of the normal ophthalmic artery flow pattern. **e** Right ophthalmic artery CDFI at one week after CAS. **f** Right ophthalmic artery CDFI at one month after CAS. **g** Right ophthalmic artery CDFI at 3 months after CAS.

right retinal artery pressure rose to 65 mm Hg, right arm-to-retina circulation time shortened to 19 s, and the right side optic fundi showed normal findings. The patient was followed up for 2.8 years after CAS, and there were no ischemic events, including visual symptoms.

Discussion

Occlusive internal carotid artery diseases exhibit ophthalmic artery flow disturbance [14]. The hemodynamic reduction of the ocular circulation due to severe internal carotid artery stenosis causes ocular ischemic syndrome. Therefore, it is significant to evaluate ophthalmic artery flow in the patients with internal carotid artery stenosis treated with CAS. The authors previously reported the effect of carotid endarterectomy on ophthalmic artery flow and ocular ischemic syndrome [15, 16]. However, there have been few reports about the effect of CAS on ocular circulation [17, 18]. To evaluate the effect of CAS on the ophthalmic artery flow, the authors examined the ophthalmic artery CDFI before and after CAS, including the follow-up period.

In the present series, 13 patients showed reversed ophthalmic artery flow before CAS. In these patients, the ophthalmic artery might function as collateral circulation from the extracranial to the intracranial circulation [19, 20]. In this series, there was a significant relationship between the degree of stenosis and the ophthalmic artery flow direction. Therefore, the flow of the ophthalmic artery as a collateral pathway for intracranial circulation depends on the degree of the primary carotid artery stenosis. The authors demonstrated the significantly increased flow velocity and correction of the flow direction in all patients immediately after CAS. This significant improvement also explains the correction of the ocular hemodynamic compromise.

In the present study, a negative correlation was demonstrated between the degree of the internal carotid artery stenosis and ophthalmic artery peak systolic flow velocity. The progress of the internal carotid artery stenosis revealed a stepwise decrease of the ophthalmic artery flow. Ultimately, the ophthalmic artery flow direction became reversed. Disturbance of the ophthalmic artery flow due to the progress of the internal carotid artery stenosis could be affected by the ipsilateral external carotid artery flow and the degree of stenosis of the contralateral internal carotid artery. In the present series, patients with contralateral internal carotid artery occlusion or more than 50% stenosis showed significantly more serious ophthalmic artery flow disturbance than patients without contralateral internal carotid artery stenosis or even those with less than 50% stenosis. However, in the present series, there were no patients showing significant stenosis of the ipsilateral external carotid artery. The effect of ipsilateral external carotid artery stenosis could not be clarified by the presenting study.

Reversed ophthalmic artery flow seen in the patients with severe carotid artery stenosis may contribute to the development of ocular ischemic syndrome [11, 21]. The reversed flow was significantly seen in the patients showing the chronic ocular ischemic syndrome before CAS in this series. For patients with chronic ocular ischemic syndrome due to reversed flow, it is vital to develop normal flow to prevent ocular ischemia [22]. In this series, 8 patients showed the chronic ocular ischemic syndrome. Among them, 6 patients initially showed the reversed ophthalmic artery flow. After CAS, all 6 patients showed normal flow. Therefore, CAS is the appropriate treatment for patients with ocular ischemic syndrome caused by reversed ophthalmic artery flow due to severe internal carotid artery stenosis. The other 2 patients with chronic ocular ischemic syndrome showed antegrade ophthalmic artery flow with reduction of peak systolic flow velocity before CAS. In these 2 patients, peak systolic flow velocity significantly increased immediately after CAS procedure. Seven patients showed an improvement of visual symptoms after CAS. Only one patient failed to show improvement of chronic ocular ischemic syndrome, due to the irreversible optic apparatus lesion. The authors report clear evidence of the effect of CAS on the improvement and prevention of chronic ocular ischemia due to internal carotid artery stenosis, based on data obtained from ophthalmic artery CDFI and clinical symptoms. Therefore, there is a good correlation between the course of ocular ischemic syndrome and the improvement of the ophthalmic artery CDFI findings during the follow-up period. CAS is effective for the treatment and prevention of ocular ischemic syndrome and is most beneficial if performed early, before the onset of irreversible neovascular glaucoma or irreversible ischemic optic fundi [14, 17].

In this study, improvement in the peak systolic flow velocity and normalization of the reversed ophthalmic artery flow occurred within 24 h after CAS. Subsequently, there was no significant change in the ophthalmic artery peak systolic flow velocity. This effect of CAS was highly expected. The authors clarified the chronological correction of the disturbed ophthalmic artery flow direction and peak systolic flow velocity after CAS based on the ophthalmic artery CDFI findings. The ophthalmic artery CDFI provides clear evidences of hemodynamic compromise in occlusive internal carotid artery lesions.

Cerebral hyperperfusion syndrome after CAS is a serious complication [23, 24]. Fortunately, in the authors' series, none of the patients showed hyperperfusion syndrome or hyperperfusion phenomenon perioperatively. The authors examined the ophthalmic artery flow within 24 h after CAS. During this period, the mean ophthalmic artery peak systolic flow velocity was not significantly higher than the control value in each group. One week after CAS, the mean ophthalmic artery peak systolic flow velocity was slightly decreased compared to the value obtained within 24 h. However, this decrease was not significant. Thus, there was a tendency toward slight hyperperfusion phenomenon but no significant hyperperfusion phenomenon in the ophthalmic artery flow velocity within 24 h after CAS in this study. This study was a very small series, and therefore these data are preliminary. In the future, a hyperperfusion phenomenon may be seen in the ophthalmic artery CDFI within 24 h after CAS in a large series. Therefore, management and prevention of hyperperfusion phenomenon of the ophthalmic artery flow after CAS should be kept in mind.

Conclusion

CAS achieved normalization of the disturbed ophthalmic artery flow, whether the flow direction of the ophthalmic artery was reversed or antegrade, immediately after CAS procedure. CAS improved the chronic ocular ischemic syndrome revealed from the severe carotid artery stenosis, and it also prevented the progress and onset of the chronic ocular ischemic syndrome.

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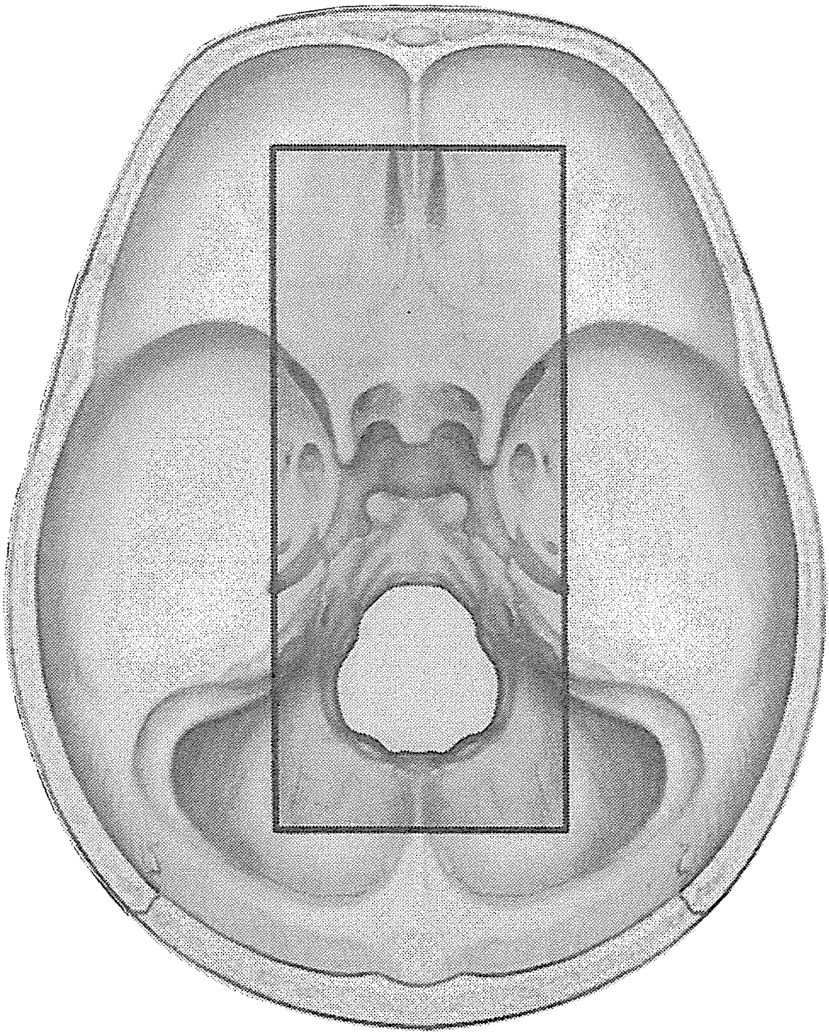

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Hemichorea due to hemodynamic ischemia associated with extracranial carotid artery stenosis

Report of two cases

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In this paper the authors describe two patients with recurrent hemiparesis and limb shaking that gradually progressed to hemichorea. Cerebral angiography confirmed severe unilateral internal carotid artery stenosis (95%) contralateral to the hemichorea. The cerebral blood flow, assessed using *N*-isopropyl-p-(iodine-123) iodoamphetamine single-photon emission computed tomography (SPECT), disclosed markedly decreased vascular reserves in both patients. After carotid endarterectomy was performed, the hemichorea gradually subsided and SPECT confirmed increased cerebral perfusion. The results in these cases indicate that surgical revascularization is effective for hemichorea due to cerebral ischemia with reduced vascular reserve.

KEY WORDS • **carotid endarterectomy** • **carotid artery stenosis** • **hemichorea** • **cerebral blood flow**

INVOLUNTARY limb shaking is an unusual manifestation of transient ischemic attacks associated with carotid artery occlusive disease; it usually lasts up to 60 seconds.[1–3,5–7,9,11–18,20,21,23,26,27,29,30,32–34] In patients with HCHB, another uncommon movement disorder, the involuntary movements are usually continuous and last for weeks or months.[4,18,19] Lesions in the contralateral caudate nucleus, putamen, thalamus, subthalamus, pons, midbrain, or subcortical white matter are thought to be responsible for such movement disorders.[19] In HCHB, the lesion can be located anywhere in the cortico-striato-pallido-thalamo-cortical feedback loop.[8,11] Hemichorea–hemiballism associated with carotid artery occlusive disease is extremely rare: its origin and surgical treatment remain controversial because there is not enough knowledge regarding the cerebral hemodynamic insufficiency in these patients.

In this report we evaluate the CBF in two patients suffering from hemichorea and severe extracranial carotid artery stenosis by using ^{123}I-IMP SPECT, and we discuss the efficacy of surgical treatment. This is the first at-rest, acetazolamide-enhanced SPECT study performed before and after CEA to assess the contribution of hemodynamic factors to the development of hemichorea associated with severe ICA stenosis.

Abbreviations used in this paper: CBF = cerebral blood flow; CEA = carotid endarterectomy; ECA = external carotid artery; HCHB = hemichorea–hemiballism; ICA = internal carotid artery; ^{123}I-IMP = *N*-isopropyl-p-(iodine-123) iodoamphetamine; MR = magnetic resonance; SPECT = single-photon emission computed tomography.

Case Reports

Case 1

History. This 75-year-old right-handed man with hypertension, hypercholesterolemia, and a 50-year history of smoking suddenly experienced recurrent transient left hemiparesis. The episodes, which occurred once or twice a week, involved only his left arm and lasted a few seconds. There were no provocative factors. He had no history of convulsive disease, orthostatic hypotension, diabetes mellitus, or parkinsonism. Involuntary continuous trembling of his left arm appeared 1 month after the onset of his first transient ischemic attack; it disappeared during sleep and could be voluntarily suppressed for only a short time. He was admitted to our hospital for further examination.

Examination. On admission, the patient was alert. There was very mild upper hemiparesis of his left arm and mild bilateral dysfunction of vibration sensation. There were no carotid artery bruits. In the pronated and supinated positions, the distal portion of his left arm twitched or jerked rapidly; the distal portion of his leg on the same side also shook. His gait was slightly disturbed because of clumsy choreiform left leg movements. The involuntary movements were diagnosed as hemichorea by a neurologist. There was no involuntary movement of the facial muscles.

Axial T_2-weighted MR images revealed small areas of hyperintensity in the bilateral corona radiata (Fig. 1). A right carotid artery angiogram demonstrated severe stenosis (95%) of the right ICA (Fig. 2A) and slow filling of the intracranial arteries (Fig. 2B and C). At-rest ^{123}I-IMP SPECT showed severe hypoperfusion within the right hemisphere (Fig. 3A and D). After acetazolamide was administered, SPECT studies were obtained that revealed a marked decrease in the vascular reserve capacity in the right hemisphere including the basal ganglia (Fig. 3B and E).

Operation and Postoperative Course. After a right CEA had been performed, we obtained SPECT studies, which demonstrated improvement in the CBF in the right hemisphere including the basal ganglia (Fig. 3C and F). At 3 months post-CEA, the hemichorea in the patient's left upper and lower limbs had ceased at rest; it disappeared completely by 2 years.

Case 2

History. This 77-year-old woman was admitted to our hospital for evaluation of ICA stenosis demonstrated on MR angiography performed elsewhere. Her history was notable for hypertension, noninsulin-dependent diabetes mellitus, chronic occlusive pulmonary disease, and hypercholesterolemia, but not for convulsive disease, orthostatic hypotension, or parkinsonism.

Examination. On admission the patient was alert and without neurological deficits except that her left leg shook intermittently for a few minutes at a time. The involuntary limb movement was transient, brief, and occurred several times a day; during the attacks, the distal portion of her left leg pronated and supinated for approximately 2 or 3 minutes and then the shaking stopped. There were no provocative factors. Over the course of the next 3 months the involuntary left limb shaking progressed to hemichorea when she was awake.

Areas of hyperintensity in the head of the caudate nucleus on the right side, bilateral basal ganglia, and centrum semiovale were demonstrated on T_2-weighted MR images (Fig. 4). A right carotid artery angiogram showed severe stenosis (95%) of the right ICA (Fig. 5A) and slow filling of the intracranial arteries on the same side (Fig. 5B and C). At-rest SPECT disclosed severe hypoperfusion within the right hemisphere including the basal ganglia (Fig. 6A and D). After acetazolamide was administered, SPECT studies demonstrated a marked decrease in vascular reserve capacity in the right hemisphere including the basal ganglia (Fig. 6B and E).

Operation and Postoperative Course. The patient underwent CEA 3 months after the deterioration of her symptoms; subsequently, her hemichorea slowly subsided. Postoperative SPECT demonstrated improved CBF in the right hemisphere including the basal ganglia (Fig. 6C and F). Her hemichorea gradually improved and is apparent only in her gait 18 months after CEA.

Discussion

We describe two patients whose hemichorea due to a decrease in CBF and vascular reserves in the contralateral hemisphere was associated with ICA stenosis. Because the involuntary movements occurred subsequent to recurrent hemiparesis or intermittent limb shaking, we suspected hemodynamic factors. Our results suggest that hemichorea occurs during the development of hemispheric hypoperfusion and that revascularization may alleviate this symptom.

Our search of the literature found only three earlier reports of HCHB associated with major extracranial atheromatous ICA stenosis.[8,23,25] In two patients, HCHB showed marked improvement after CEA.[23,25] In another patient, the hemichorea gradually subsided naturally; however, there was an incremental worsening of hemiparesis.[8] The patient in our Case 1 experienced recurrent transient hemiparesis that progressed to hemichorea, suggesting that increasing involvement of the premotor cortex or corticostriatal fibers resulted in hemichorea. Although an association between moyamoya disease and hemichorea has been reported,[10,11,22,24,28,31] only a few patients described underwent surgical reconstruction.[10,11,22,31] After these patients had undergone an ECA–ICA bypass, their hemichorea subsided or disappeared slowly as their CBF normalized. These results suggest that impaired CBF may be an important contributing

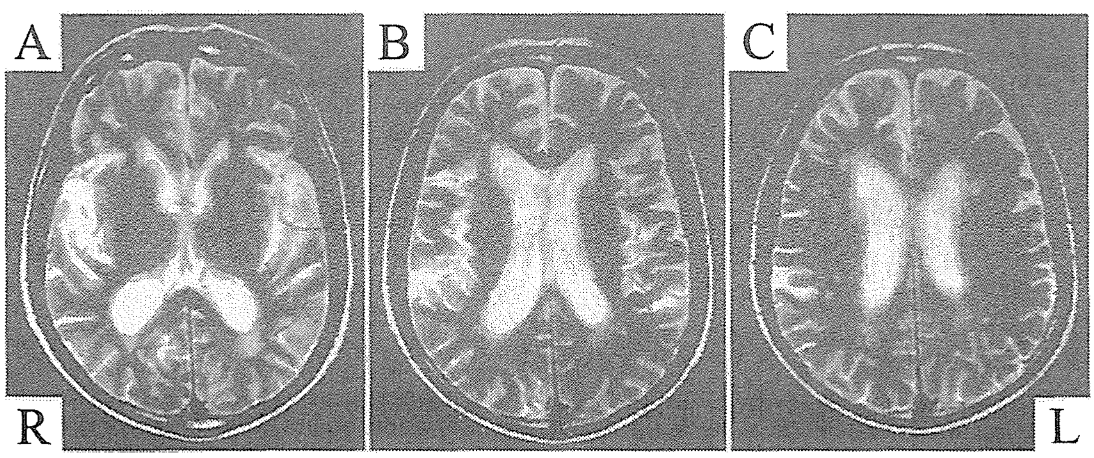

FIG. 1. Case 1. Axial T_2-weighted MR images obtained at admission, showing small areas of high signal intensity in the bilateral corona radiata. L = left; R = right.

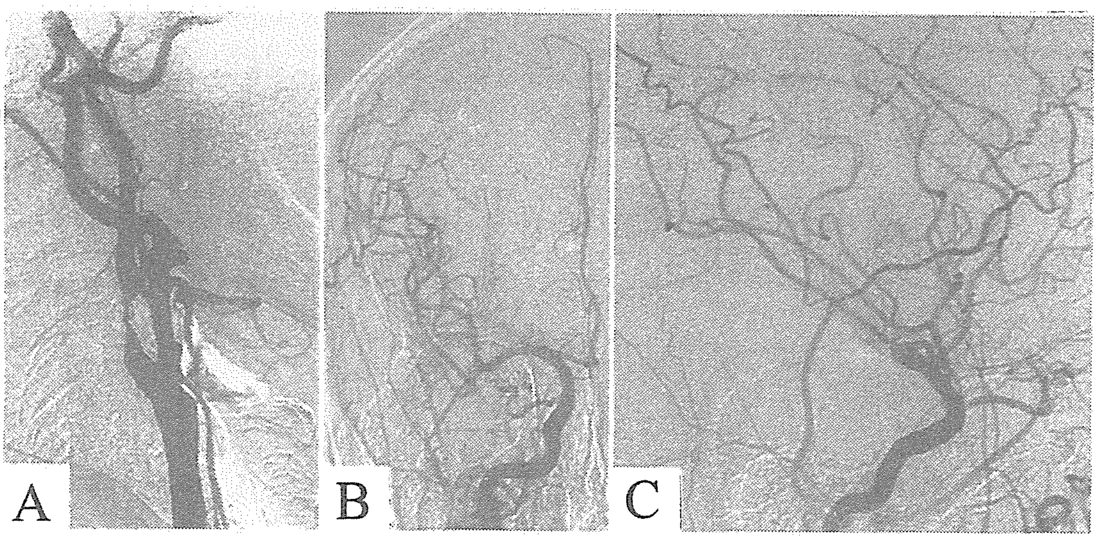

FIG. 2. Case 1. A: Right carotid artery angiogram showing severe stenosis of the ICA. B and C: Right carotid artery angiograms demonstrating delayed blood flow to the intracranial circulation (A and C, lateral views; B, anteroposterior view).

factor in hemichorea associated with intracranial ICA stenosis.

It has been reported that HCHB may occur in patients whose areas of ischemia are located within the cortico-striato-pallido-thalamo-cortical feedback loop.[8,11] The infarct sites, where CBF is thought to be most severely impaired, and the region of the perfusion defect and decreased reserves must be considered, because the reversible involun-

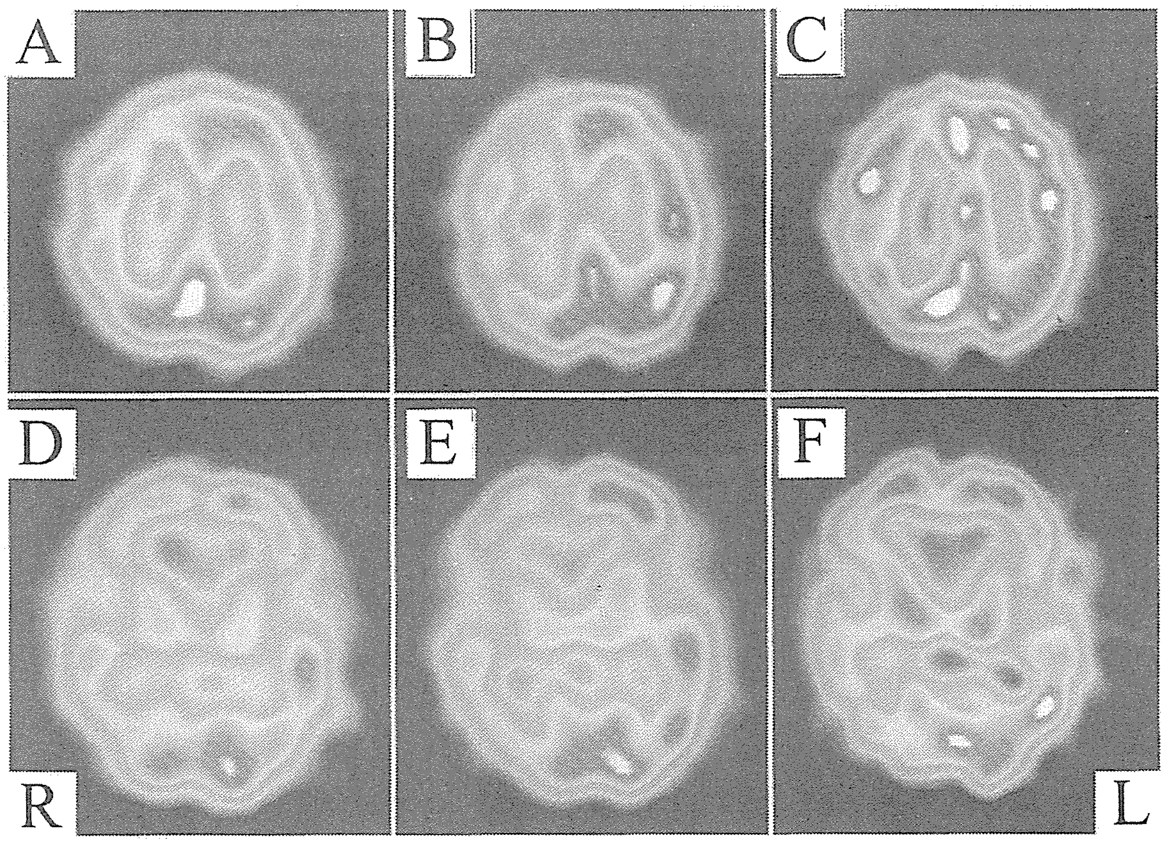

FIG. 3. Case 1. A and D: Preoperative ^{123}I-IMP SPECT scans demonstrating severe hypoperfusion in the right hemisphere including the basal ganglia. B and E: Preoperative ^{123}I-IMP SPECT scans obtained after acetazolamide infusion, showing a marked decrease in the vascular reserve in the right hemisphere including the basal ganglia. C and F: Postoperative ^{123}I-IMP SPECT scans demonstrating improvement in the CBF in the right hemisphere including the basal ganglia.

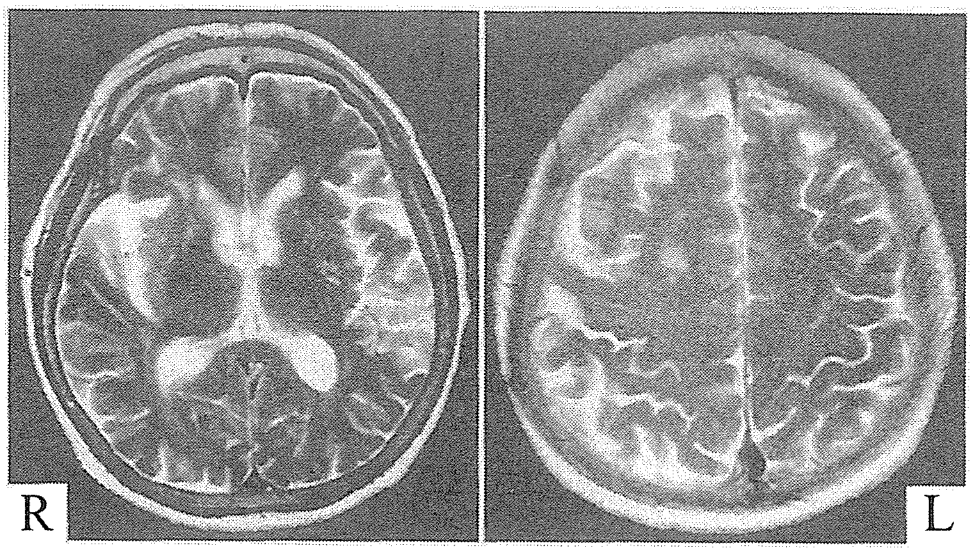

FIG. 4. Case 2. Axial T_2-weighted MR images obtained at admission, showing small areas of high signal intensity in the right white matter in the frontal lobe and bilateral basal ganglia.

tary movements differed in earlier reports in patients with HCHB associated with carotid occlusive disease. Many infarcts occur in the frontal subcortical white matter[8,10,11,25,27] and basal ganglia infarcts are relatively rare.[10,23,25] Although in earlier reports the area of decreased CBF varied from the cortex to the basal ganglia,[8,10,11,25] the region of decreased vascular reserves involved the frontal lobe in two of three cases.[10,11] This suggests that lesions on the anterior border zone are associated with the greatest consequence. The infarcts in our patients were located in the deep anterior watershed (Case 1) and the frontal centrum semiovale and basal ganglia (Case 2), regions considered to lie within the anterior watershed area. The regions of decreased perfusion and autoregulatory reserve were hemispheric. Our results support the hypothesis that connecting fibers in the superficial or deep anterior watershed were exposed to ischemic conditions and that the selective disruption of corticostriatal projections from the indirect pathway resulted in the hemichorea observed in our patients.

Conservative medical therapies have been attempted in patients with limb shaking. Administration of antiplatelet agents and lowering the dose or discontinuing administration of antihypertension agents have resulted in marked improvement in some cases.[1,2,16,23,30] Anticonvulsion agents and levodopa have been ineffective in most patients.[1,2,12,32,34] The most common and effective treatments are surgical revascularization, for example, CEA,[1,2,14,20,29,32,33] CEA specific to the ECA,[14,33,34] and ECA–ICA bypass surgery.[1,5,7,9,11,13,32,33] In

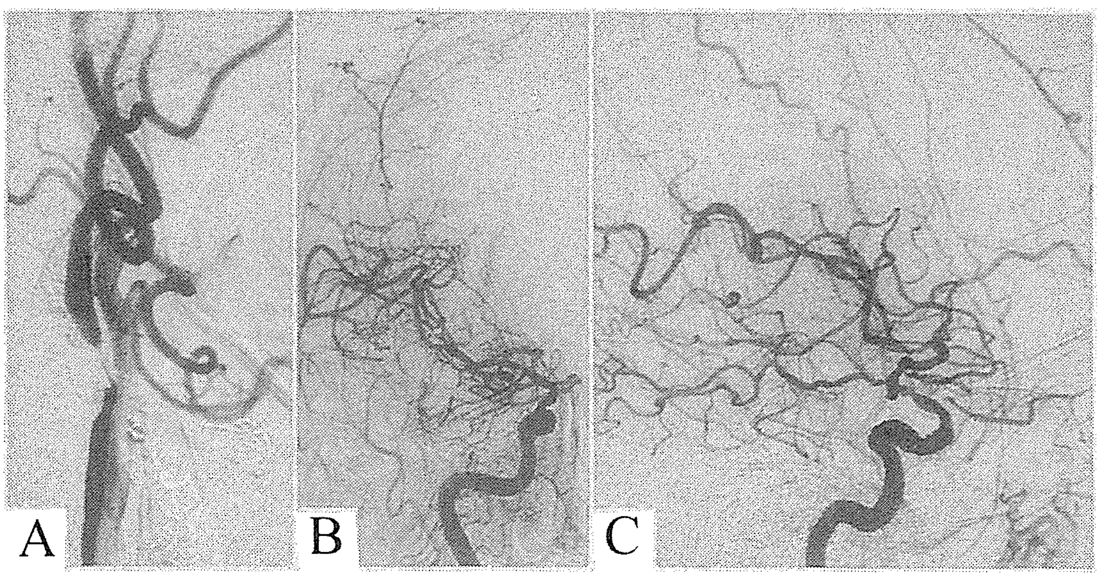

FIG. 5. Case 2. A: Right carotid aftery angiogram demonstrating severe carotid artery stenosis. B and C: Right carotid artery angiograms showing stenosis of the ICA at the supraclinoid portion and slow filling of the intracranial middle cerebral artery (A and C, lateral views; B, anteroposterior view).

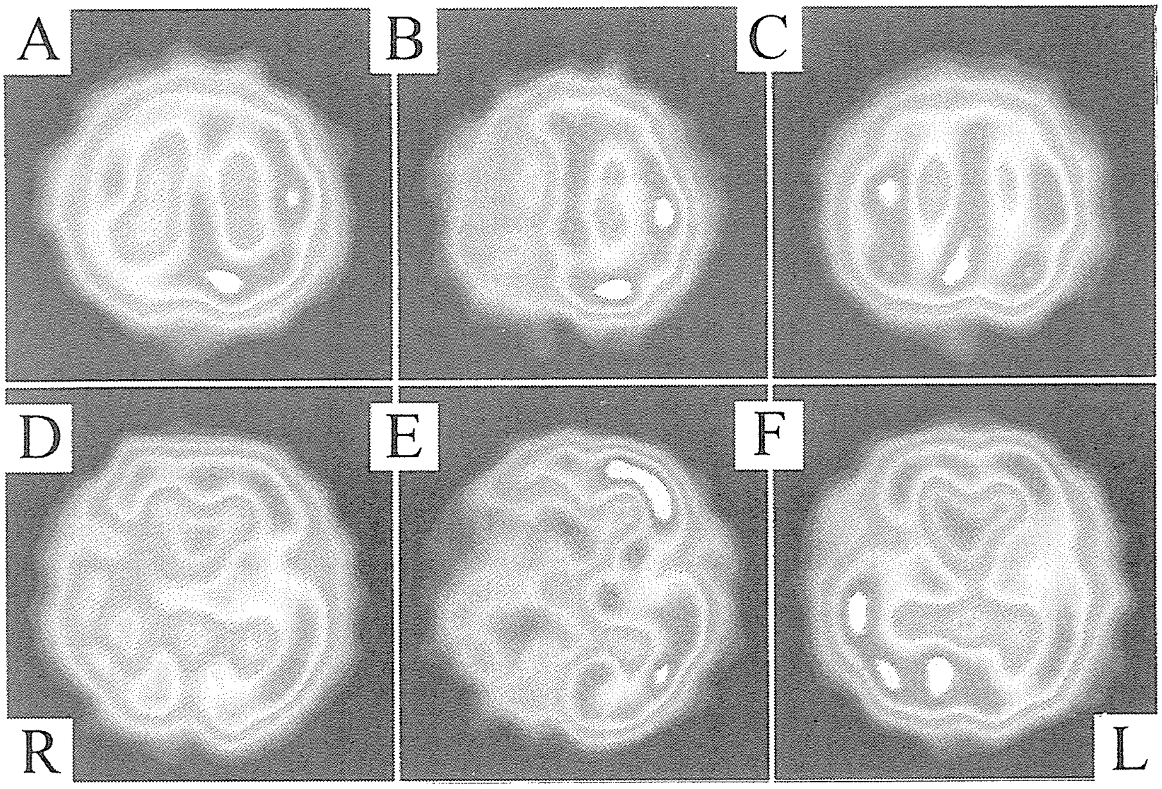

FIG. 6. Case 2. A and D: Preoperative ^{123}I-IMP SPECT scans showing severe hypoperfusion in the right hemisphere including the basal ganglia. B and E: Preoperative ^{123}I-IMP SPECT scans obtained after acetazolamide infusion, revealing a marked decrease in vascular reserve in the right hemisphere including the basal ganglia. C and F: Postoperative ^{123}I-IMP SPECT scans demonstrating improved CBF in the right hemisphere including the basal ganglia.

some patients with spontaneous collateral compensation, a natural cure is obtained, whereas in others the condition may progress to hemichorea. Although in many patients infarct lesions appeared in the frontal white matter,[1,2,7,11,30,33,34] in others there were no lesions.[1,2,14,29,32,33] The region involved in the perfusion defect frequently includes the frontoparietal lobes,[6,7,11,12,29,30,34] and decreased vascular reserves are often hemispheric.[2,5,7,12,14] There is some evidence for a correlation between limb shaking and ischemia in the anterior border zone. We suggest that decreased vascular reserves constitute a risk factor for the progression of limb shaking to HCHB. In addition we stress that before undertaking any revascularization procedures, the status of a patient's cerebrovascular reserves must be determined.

We propose that the mechanism underlying the development of hemichorea associated with carotid artery occlusive disease is strongly correlated with ischemia in the anterior border zone and that surgical revascularization is an effective therapy in these patients. Cytotoxic edema appears to be an unlikely candidate for the cause of treatable involuntary movements in our Case 2 because the patient's leg shaking continued for 3 months and gradually worsened in the absence of further infarctions.

Conclusions

We describe two patients with severe hemodynamic ischemia due to severe carotid artery stenosis who manifested hemichorea. Carotid endarterectomy effectively improved this rare disorder and normalized the CBF.

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