



Clinicoradiological Features and Outcomes of Patients with Atherosclerotic Basilar Artery Steno-Occlusion: A Single-Center Experience

뇌저동맥 협착-폐색의 임상-영상의학적 특징과 결과: 단일 기관 연구

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Purpose: There is a relatively higher risk of peri-procedural stroke following elective stenting of patients with basilar artery (BA) occlusion compared with stenting of intracranial arteries. We sought to diagnose stroke risks in patients with BA steno-occlusive disease by describing their clinicoradiological features and by demonstrating that appropriate treatment would lead to favorable outcomes.

Materials and Methods: A total of 92 patients who were treated from 2004 to 2016 for severe stenosis or occlusion of BA based on MR or CT angiography were enrolled in the study. We assessed clinical features, radiologic findings, and other clinical outcomes such as the degree of disability as determined by the modified Rankin Scale.

Results: A total of 49 of the 92 patients (53.3%) had no relevant symptoms. The risk of a recurrent or new infarct in the relevant area was 4.59%/year. Following treatment, more than 50% of the 92 patients had favorable outcomes. A recurrent or new infarct was found in 9 (20.5%) of the 44 patients who had a poor prognosis. There was no significant difference between the two groups with respect to compromised circulation; however, the initial infarct (16 of 48 and 29 of 44, $p = 0.002$) was statistically significant between the two groups.

Conclusion: Atherosclerotic BA steno-occlusion disease is associated with a relatively low risk of a recurrent or new infarct and with favorable clinical outcomes following appropriate medical treatment.

Index terms

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INTRODUCTION

Atherosclerotic steno-occlusive disease of intracranial arteries is one of the most common causes of ischemic strokes; ongoing debates center around treatment options (1-3). A recent clinical trial, the Stenting and Aggressive Medical Management for Preventing Recurrent stroke in Intracranial Stenosis (SAMMPRIS) study by Derdeyn et al. (4), showed that early, aggressive medical management is more beneficial than stenting for high-risk patients with atherosclerotic intracranial stenosis, which per-

sists over an extended follow-up period. Angioplasty and stenting were associated with a higher than expected rate of perioperative stroke in this trial (5). We found vertebrobasilar artery stenosis, in particular, to be the factor with the highest hazard ratio for ischemic stroke in the region of the stented artery (6, 7). The postulated pathophysiological mechanism is perforator occlusion i.e., forceful displacement of the disrupted atheromatous debris squashed into the ostia by the stent (6, 8).

There have been a number of small studies showing that patients with vertebrobasilar artery occlusive disease had a rela-

tively benign clinical course (9-11). A possible explanation for these results may be that collateral circulation had the potential to maintain adequate perfusion to the posterior fossa after progressive stenosis (9, 11-13).

Therefore, one has to consider that there is a higher risk of peri-procedural ischemic stroke when using angioplastic procedures involving the basilar artery (BA) compared to other intracranial arteries. Since progressive steno-occlusion of the vertebralbasilar artery is associated with a benign disease course, successful medical treatment, rather than stenting, can provide the most benefit to patients with BA atherosclerotic steno-occlusive disease. This hypothesis can be tested by analyzing studies focused on medically treated atherosclerotic steno-occlusion of the BA. We obtained data regarding clinicoradiological features and outcomes of patients with BA atherosclerotic steno-occlusive disease. At follow-up visits, we also evaluated radiological factors affecting their clinical outcomes. These results will be helpful for predicting outcomes and establishing more suitable treatment strategies.

MATERIALS AND METHODS

Patients

We retrospectively reviewed the clinical and imaging database of 132 symptomatic or asymptomatic patients diagnosed with steno-occlusive disease of the BA. These patients were admitted to or had visited a tertiary hospital between January 2004 and July 2016 and had available follow-up data for more than two months. This study was approved by the Institutional Review Board of Hanyang University Seoul hospital (IRB file No. 2016-08-14) and written informed consent was obtained from all patients. The following inclusion criteria were used for this study: severe stenosis (> 70% narrowing of luminal diameter) or occlusion (i.e., invisible lumen) of the BA based on MR or CT angiography (by means of time-of-flight and contrast material-enhanced angiography). Patients were excluded if they had acute non-atherosclerotic causes of BA steno-occlusion, such as dissection, and a cardiac source of the embolus. Other exclusion criteria included intra-arterial thrombolysis or elective primary angioplasty, and stent placement. On the basis of these criteria, we excluded 12 patients with non-atherosclerotic causes, of which dissection was the most common cause; 7 pa-

tients were excluded with high-risk cardio-embolic factors; 19 patients had no follow-up data; and 2 patients with primary thrombolytic had undergone stent placements. Thus, 92 medically treated patients with atherosclerotic BA steno-occlusion were included in the final analysis. Upon diagnosis of atherosclerotic intracranial steno-occlusive disease, patients were treated using management of the primary risk factors and administration of antiplatelets asymptomatic patients took a single therapy with aspirin (the Aspirin Protect[®] Tab, Bayer AG, Leverkusen, Germany, 100 mg × 1 TAB/day). Symptomatic patients received combination therapy with aspirin (the Aspirin Protect[®] Tab, 100 mg × 1 TAB/day) plus clopidogrel (Plavix[®], Sanofi Winthrop Industrie, Carbon Blanc, France, 75 mg × 1 TAB/day) or aspirin (Aspirin Protect[®] Tab, 100 mg × 1 TAB/day) plus cilostazol (Pletal[®], Otsuka Pharmaceutical Co., Tokushima, Japan, 50 mg × 0.5 TAB/day).

Clinical Evaluation

We documented patient demographics, including sex, age, risk factors, and clinical presentations. The clinical presentations included symptoms associated with transient ischemic attack or stroke, including dizziness, dysarthria or diplopia, weakness of the extremities, and “top of the basilar syndrome.” We considered people with BA stenosis or occlusion detected incidentally on CT or MR angiography for other symptoms unrelated to vertebralbasilar insufficiency or health care to be asymptomatic. We defined the risk factors for intracranial arterial stenosis as follows: 1) diabetes mellitus if we observed the use of hypoglycemic drugs, a random glucose level ≥ 200 mg/dL, or glycosylated hemoglobin level $\geq 6.4\%$ upon admission, 2) hypertension if the patient had a history of antihypertensive medication use, a systolic blood pressure ≥ 140 mm Hg, or a diastolic blood pressure ≥ 90 mm Hg, 3) hyperlipidemia if the patient mentioned a history of the use of anti-hyperlipidemic agents or had a serum cholesterol level of ≥ 220 mg/dL, and 4) smoking, whatever the level of consumption.

During the follow-up period, we evaluated each patient clinically or radiologically for the presence of a recurrent or new infarct and calculated the annual risk of recurrent or new infarct. We determined the clinical outcomes using the modified Rankin Scale (mRS) at both the initial detection time and at the last follow-up appointment. We recorded the mRS score after conduct-

ing a review by phone of each medical record. We defined a favorable outcome as an mRS score ≤ 2 (i.e., unable to carry out all previous activities, but able to look after own affairs without assistance). We defined a poor outcome (overall poor outcome) as an mRS score ≥ 3 (i.e., requiring some help, but able to walk without assistance). We considered an outcome to be relevant when clinical symptoms and outcomes were correlated with radiologic findings at the last follow-up examination. That is, among patients with poor prognosis, we excluded those who had other causes that could affect the clinical outcome, such as anterior circulation infarction, cancer, or trauma other than posterior circulation ischemia, from the relevant poor-outcome group.

Radiological Evaluation

We performed MR imaging using a 3T system (Achieva; Philips Healthcare, Best, Netherlands) and a phased array head coil with sensitivity encoding. We obtained time-of-flight MR angiograms and contrast material-enhanced angiography as well as conventional MR images. A 64-slice computed tomography scanner (Brilliance CT 64 Slice, Siemens, Forchheim, Germany) for CT angiography. We reviewed the images using reformats and maximum intensity projections in multiple planes. For situations in which we could not precisely evaluate the degree or underlying pathologic disease of BA steno-occlusion on MR or CT angiography, we confirmed and distinguished intracranial dissection from atherosclerosis using high-resolution MR imaging (HRMRI) or catheter angiography. We performed

HRMRI for the evaluation of the vessel wall using two-dimensional proton density-weighted imaging and the black-blood technique, which was available for 30 patients.

We evaluated the anatomical characteristics of BA steno-occlusion, including the length and location of the stenosis or occlusion of the BA. We subdivided the lengths of steno-occlusion of the BA into shorter (i.e., shorter than half of the BA's total length) or longer (i.e., longer than half of the BA's total length) lesions. We divided the BA into three equal segments (i.e., proximal, mid, and distal) to determine the range of stenosis or occlusion. We subdivided the location of steno-occlusion into proximal-and-middle, distal, and the whole length of the BA. We recorded the absence or presence of the posterior communicating artery (PCoM), vertebral artery (VA) hypoplasia, and steno-occlusive lesions in the VA. We defined VA hypoplasia using the fourth vertebral segment diameter of ≤ 2.0 mm and a concomitant diameter asymmetry ratio of $\leq 1:1.7$ in all of the four vertebral segments. We defined VA steno-occlusion by the luminal diameter of $> 50\%$ narrowing or no visible lumen at any site of the VA (Fig. 1).

We first reviewed the radiological images separately and then discussed them until consensus was reached by two radiologists (L.Y.-J and S.G.H) for the discrepant cases.

Statistics

We used the chi-squared test for comparison of clinical presentations, radiological findings, recurrent infarct rates, and clini-

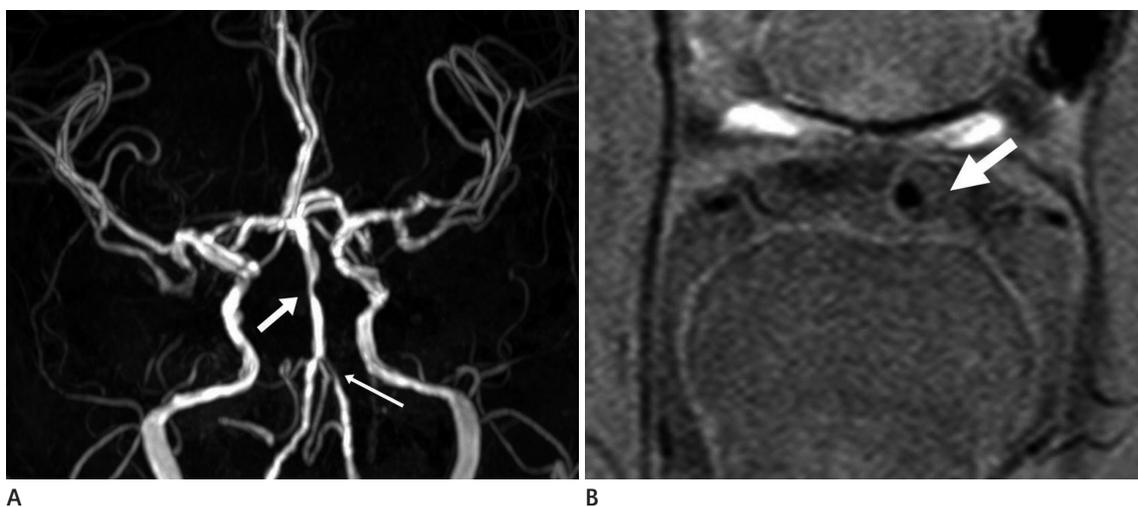


Fig. 1. Basilar artery stenosis due to atherosclerosis. An MR angiogram (**A**) shows a short stenosis at the middle basilar artery (short arrow). A proton density-weighted high-resolution MR image (**B**) shows eccentric wall thickening (arrow) at the middle basilar artery, which may be indicative of an atherosclerotic plaque. In an MR angiogram (**A**), the stenosis at the fourth segment of vertebral artery (long arrow), left is also noted.

cal outcomes between the symptomatic and asymptomatic groups and between the favorable and poor outcome groups. We defined the statistical significance threshold as a p -value < 0.05 .

RESULTS

The study group consisted of 37 men (40.2%) and 55 women (59.8%) with a mean age of 74.0 years (median: 70.5 years; range: 48–93 years). On average, men presented with the steno-occlusive disease of the BA at a younger age than women (mean: 73.6 and 74.2 years, respectively). Hypertension was the most prevalent risk factor ($n = 69/92$, 75.0%). Based on MR or CT angiography, we determined that 21 patients (22.8%) had BA occlusion and 71 patients (77.2%) showed severe stenosis of the BA (Figs. 1, 2). The median duration of follow-up for all patients was 62 months (range: 2–121 months).

The clinical presentations consisted of symptoms associated with vertebrobasilar insufficiency, including dizziness, dysarthria or diplopia (36 of 92, 39.1%), weakness of the extremities (6 of 92, 6.5%), “top of the basilar syndrome” (1 of 92, 1.1%), or

no symptoms (49 of 92, 53.3%). Upon initial imaging, 45 of 92 patients (48.9%) showed a recent or chronic infarct (Table 1).

A recurrent or new infarct was found in 11 patients during the follow-up period. The annual risk of stroke of 92 patients was 4.59%/year. The annual risk of stroke of 43 symptomatic patients and 49 asymptomatic patients was 4.03%/year and 5.21%/year, respectively. There was no significant difference in recurrent or new infarct rates between symptomatic and asymptomatic patients (5 of 43, 11.6% and 6 of 49, 12.2%, respectively; $p = 0.927$). In addition, neither overall nor relevant poor outcome rates showed significant differences between symptomatic and asymptomatic patients (8 of 43, 18.6% and 14 of 49, 28.6%, respectively, for overall outcomes; $p = 0.263$ and 8 of 43, 18.6%, and 7 of 49, 14.3%, respectively, for relevant poor outcomes; $p = 0.576$) (Table 2).

A total of 48 of the 92 patients (52.2%) showed favorable clinical outcomes; 44 showed poor outcomes. Of the 44 patients with poor outcomes, 23 (52.3%) showed relevant poor outcomes. A recurrent or new infarct was found in 9 of 44 patients, with poor outcomes (20.5%) (among 23 patients with relevant poor outcomes, 39.1%), and in 2 of 48 patients, with favorable outcomes (4.2%) (Table 3). We investigated several radiologic factors that could affect their clinical outcomes, such as lesion grade, length, and location; inflow compromise (undetectable PCom, VA stenosis-occlusion and VA hypoplasia); and initial infarct. Among those factors, we found compromised inflow in the forms of

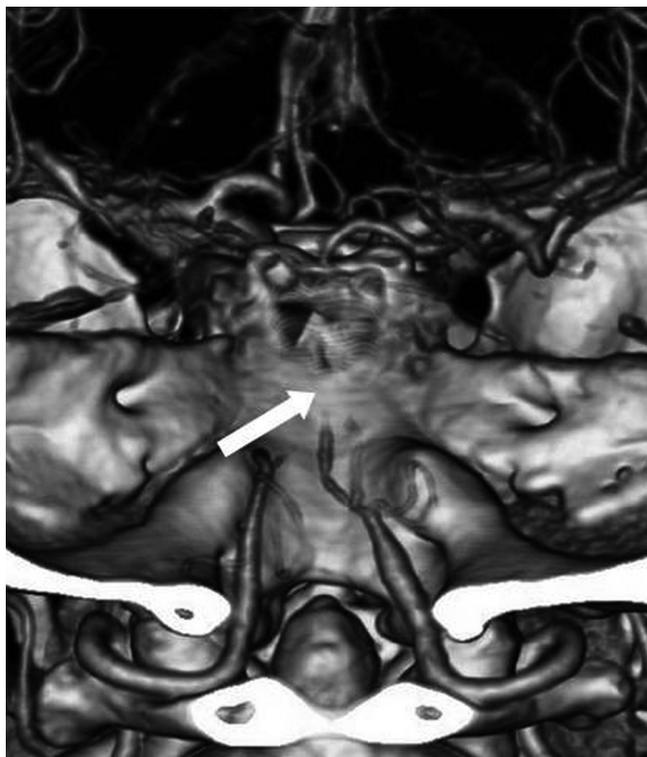


Fig. 2. Basilar artery occlusion. An CT angiogram reconstruction scan shows the entire length of the basilar artery occlusion (arrow), along with underlying vertebrobasilar hypoplasia.

Table 1. Clinicoradiological Characteristics of Patients with Basilar Artery Steno–Occlusion

Clinicoradiological Characteristics	All ($n = 92$)	p -Value
Infarct upon initial imaging, (%)		
Yes	45 (48.9)	< 0.001
No	47 (51.1)	
Clinical presentation, (%)		
Dizziness/dysarthria/diplopia	36 (39.1)	0.003
Extremity weakness	6 (6.5)	0.526
Top of basilar syndrome	1 (1.1)	0.585
No relevant symptoms	49 (53.3)	0.002
Lesion length, (%)		
Short	70 (76.1)	< 0.001
Long	22 (23.9)	
Lesion location, (%)		
Whole	14 (15.2)	< 0.001
Distal	17 (18.5)	0.229
Proximal-middle	61 (66.3)	< 0.001

Table 2. Comparison of New Infarct and Clinical Outcome between Symptomatic and Asymptomatic Patients with Atherosclerotic Basilar Artery Steno–Occlusion

	All (<i>n</i> = 92)	Symptomatic (<i>n</i> = 43)	Asymptomatic (<i>n</i> = 49)	<i>p</i> -Value
Recurrent or new infarct, (%)	11 (12.0)	5 (11.6)	6 (12.2)	0.927
Overall poor outcome, (%)	22 (23.9)	8 (18.6)	14 (28.6)	0.263
Relevant poor outcome, (%)	15 (16.3)	8 (18.6)	7 (14.3)	0.576
Inflow compromise [‡]				
Yes	61 (8/11)*	27 (3/5)*	34 (5/6)*	0.504
No	31 (3/4)*	16 (2/3)*	15 (1/1)*	

*Numbers in parenthesis are number of new infarct/number of poor outcome.

[‡]Undetectable posterior communicating artery or co-existing vertebral artery steno–occlusion.

Table 3. Radiological Characteristics of Patients with Atherosclerotic Basilar Artery Steno–Occlusion with Poor and Favorable Outcomes

Radiological Characteristics	All (<i>n</i> = 92)	Favorable Outcome (<i>n</i> = 48)	Poor Outcome			
			Overall (<i>n</i> = 44)	<i>p</i> -Value	Relevant (<i>n</i> = 23)	<i>p</i> -Value
Inflow compromise, (%)						
Undetectable PCom	35 (38.0)	21 (43.8)	14 (31.8)	0.239	10 (43.5)	0.535
VA steno–occlusion	45 (48.9)	23 (47.9)	22 (50.0)	0.842	11 (47.8)	0.904
VA hypoplasia	20 (21.7)	8 (16.7)	12 (27.3)	0.218	3 (13.0)	0.355
Infarct*, (%)	45 (48.9)	16 (33.3)	29 (65.9)	0.002	17 (73.9)	0.006
Recurrent/new infarct [‡] , (%)	11 (7/4) (12.0)	2 (0/2) (4.2)	9 (7/2) (20.5)	0.016	9 (7/2) (39.1)	< 0.001

*Recent or chronic infarct on initial examination.

[‡]Recurrent or new infarct during follow-up, numbers in parenthesis are number of recurrent infarct/number of new infarct.

PCom = posterior communicating artery, VA = vertebral artery

undetectable PCom, co-existing VA steno–occlusion and VA hypoplasia in 35 (38.0%), 45 (48.9%), and 20 (21.7%) of the 92 patients, respectively (Table 3). These values were not statistically different between the symptomatic and asymptomatic groups (27 of 43 and 34 of 49, respectively; $p = 0.504$) (Table 2) and revealed no statistically significant differences between the favorable and poor outcome groups (21 of 48, 43.8% and 14 of 44, 31.8%, respectively, for undetectable PCom; $p = 0.239$, 23 of 48, 47.9%, and 22 of 44, 50.0%, respectively, for VA steno–occlusion; $p = 0.842$ and 8 of 48, 16.7%, and 12 of 44, 27.3%, respectively, for VA hypoplasia; $p = 0.218$) (Table 3). However, infarct on initial examination was significantly associated with poor outcome ($p = 0.002$ and $p = 0/016$, respectively). These findings were similar whether overall or relevant to a poor outcome (Table 3).

DISCUSSION

Our data represent clinicrodiological features and outcomes of patients with atherosclerotic BA steno–occlusive disease from a single center. The patients with atherosclerotic BA steno–occlusive disease had relatively benign clinical symptoms over the

course of the illness; more than half of the patients were asymptomatic at presentation and everyone received treatment. Regardless of the presence or absence of symptoms, patients had relatively low disease recurrences or new infarct rates and more than 50% of the individuals had favorable clinical outcomes. Compromised inflow did not affect their initial clinical presentations or clinical outcomes. Of all the multiple radiologic factors, the initial infarct was significantly associated with a favorable or unfavorable prognosis.

The time it takes to establish collateral circulation may be one of the most important factors that affect the clinical outcomes of patients with BA steno–occlusive disease. Devuyst et al. (14) suggested that a carotid–basilar reflux, if the distal portion of the BA remained open, was one of the predictive factors of a good prognosis for BA occlusion. On the other hand, stenotic disease of the upper-third of the BA was also associated with poor clinical outcomes because stenotic disease in this region was most often caused by an embolus rather than local thrombotic lesions; consequently, there was not sufficient time for the patient to develop adequate collateral circulation (14). This was why we evaluated the location of BA steno–occlusion by dividing the locations of steno–occlusion into three segments (i.e., proximal–

and-middle, distal, and the whole length of the BA). Distal BA steno-occlusion showed less favorable outcomes than proximal-and-middle type. Better outcomes could result from the BA steno-occlusion, through sufficient revascularization strategies to establish collateral circulation. In addition, non-invasive diagnostic methods such as CT or MR angiography are now better able to detect subclinical or asymptomatic BA steno-occlusions prior to early neurologic deterioration (15). Therefore, the prognosis of BA steno-occlusion is more diverse and benign than was previously thought (14). Our study also shows more than 50% of favorable outcomes on mRS (75.0% of relevant favorable outcomes on mRS) in patients with atherosclerotic BA steno-occlusion.

In the SAMMPRIS trial by Derdeyn et al. (4), the cumulative probability of any stroke at a follow-up visit of one year was 14.9% in the medical group and 21.9% in the percutaneous transluminal angioplasty and stenting group of patients (who had a recent transient ischemic attack or stroke related to a major intracranial stenosis mostly in the anterior circulation); data focusing on BA stenosis was not available. In our study, the annual risk of a recurrent or new infarct in the 92 patients with atherosclerotic BA steno-occlusion who received only medical treatment was 4.59%/year, which is lower than that of the SAMMPRIS trial. Considering the 43 symptomatic patients, the annual risk of recurrent or new infarct was only 4.03%/year. This statistic is comparable to the study by Abuzinadah et al. (16), in which the stroke recurrence rate in the symptomatic vertebrobasilar stenosis group who were treated medically was 9.6%/year and in the endovascular group was 7.2%/year. Vertebrobasilar stenosis is associated with a stroke recurrence risk that varies between 2.5–5.5% and 10–15% per year (17). Our study supported the hypothesis that BA atherosclerotic steno-occlusion might have a relatively benign clinical course with the aid of only medical management. In keeping with this conclusion, our results showed a lower stroke recurrence rate compared to that of previous studies that supported the efficacy and safety of medical treatment over stenting.

Numerous studies have been performed to examine the prognostic factors for acute BA stroke. In a study by Poletti et al. (18), of all the CT signs analyzed for patients with BA occlusion, only the presence of signs of acute ischemia on the admission CT was associated with poor prognosis. In a recent study by Lee et

al. (19), for medically treated symptomatic BA stenosis, MR imaging parameters such as hyperintense proximal BA at fluid-attenuated inversion recovery imaging and the diffusion weighted posterior circulation Alberta Stroke Program Early CT Score had independent prognostic values for early neurologic deterioration and long-term outcomes. We discovered that the presence of an initial infarct lesion on imaging scans was statistically different in favorable and poor outcome groups and could be radiologic prognostic factors for medically treated patients with atherosclerotic BA steno-occlusion. This result will help to establish management strategies for atherosclerotic BA steno-occlusion. However, further study to search for multiple radiologic predictors for clinical outcomes of patients with BA steno-occlusion is required.

A few limitations of the present study should be addressed. First, we could not confirm all of the BA steno-occlusion via catheter angiography; there might be an over or underestimation of steno-occlusion in our patients caused by the inherent limited resolution or presence of artifacts in CT or MR angiography. MR angiography is known to overestimate stenosis more often than CT angiography (20). However, Caplan (13) used MR angiography to image BA stenosis in patients with strokes and supported this diagnostic tool for stroke in the posterior circulation. We tried to overcome the limitation of CT or MR angiography by acquiring HRMRI scans and digital subtraction angiography in the cases in which insufficient evaluation was done using only CT or MR angiography. The second limitation is the possibility that two or more radiologic factors with mutual correlation might have reduced their own statistical significance, which might have limited the statistical reliability for comparison between patients with poor and favorable outcomes. Third, we applied mRS to not only patients with stroke but also patients prior to stroke attack. A mRS is generally used in the clinical setting of acute stroke. However, the study by Fearon et al. (21) encouraged prestroke mRS assessment in combination with co-morbidity or other functional impairment indices as an alternative to mRS in the case of stroke although relying on prestroke mRS alone might be suboptimal. On the assumption that prestroke mRS would produce significant reliability as an index for clinical outcomes, we tried to assure the reliability of our mRS assessments by considering critical co-morbidities that would affect the functional impairment

and increase the mRS score.

In conclusion, our study demonstrated that patients with atherosclerotic BA steno-occlusion have a relatively low annual risk of recurrent or new infarct and have favorable outcomes when they receive appropriate medical treatment. Given these data and considering the higher peri-procedural risk in procedures involving BA steno-occlusion compared to procedures involving anterior circulation, medical treatment would be preferred over stenting in patients with atherosclerotic BA steno-occlusion.

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뇌저동맥 협착-폐색의 임상-영상의학적 특징과 결과: 단일 기관 연구

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목적: 다른 대뇌 동맥들과 비교하여 뇌기저동맥 협착 또는 폐색 부위에 스텐트 삽입 시 뇌경색 발생률이 비교적 높다. 이 연구는 약물 치료만 받은 동맥 경화성 뇌기저동맥 협착 및 폐색 환자들의 임상적-영상의학적 특징 및 뇌경색의 위험 정도를 파악하여 약물 치료만으로도 비교적 좋은 예후를 보일 수 있음을 알아보고자 한다.

대상과 방법: 2004년부터 2016년에 걸쳐 MR or CT angiography에서 뇌기저동맥에 심각한 동맥 경화성 협착(70% 이상)과 폐색을 보인 환자 중 약물 치료만 받은 92명을 대상으로 하였다. 그들의 임상적-영상의학적 특징과 예후를 평가 하였다.

결과: 92명 중 49명(53.3%)이 처음 내원 당시 뚜렷한 증상이 없었다. 추적 기간 중 뇌경색이 재발하거나 새로 발생된 비율은 4.59%/년이었고, 50% 이상의 환자들은 신경학적 척도 검사상 비교적 좋은 예후를 보였다. 나쁜 예후를 보인 44명의 환자 중 9명(20.5%)에서 뇌경색이 재발하거나 새로 생겼다. 혈류의 흐름을 방해하는 요소들은 좋은 예후군과 나쁜 예후군 사이에서 통계적으로 의미 있는 차이를 보이지 못했다. 그러나 초기 평가 당시 동반된 뇌경색(16 of 48 vs. 29 of 44, $p = 0.002$)은 두 군 사이에 통계적으로 의미 있는 차이를 보였다.

결론: 동맥 경화성 뇌기저동맥 협착 또는 폐색을 보인 환자들은 적절한 약물 치료로 상대적으로 낮은 재경색 발생률과 좋은 예후를 보인다.

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