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One-Year Prognosis and Outcome according to Age with Lateral Medullary Infarction

외측 연수 경색에서 연령에 따른 1 년의 예후 및 결과

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ABSTRACT

Introduction: Few studies have compared stroke mechanisms and prognosis in lateral medullary infarction (LMI) between young and old patients. Here, I investigated the differences in the risk factors, etiologies, and prognosis between young and old patients with LMI.

Materials and Methods: I reviewed retrospectively consecutive patients with acute LMI who were admitted within 7 days after symptom onset between February 2004 and January 2011. Neurological outcomes I measured by Barthel Index (BI) and Modified Rankin Scale (mRS) at 1 year, and clinical events were checked for 1 year. Patients were divided into two groups according to their age: 18-59 years (young age group), and over 60 years (old age group). I also divided the patients into two groups with favorable outcome (mRS score 0-1 and BI 95-100) and unfavorable outcome (mRS score ≥2 and BI <95). I performed Brain MR angiography (MRA) or conventional angiography to evaluate vascular pathologies.

Results: A total of 106 patients were included in the study, of whom 37 were considered young patients (age, 18–59 years) and 69 were considered old patients (age, 60≥ years). The most common etiologic mechanism observed in this study was large artery atherosclerosis, which was observed in both groups (young group, 45.9%; old group, 75.4%). Arterial dissection and small vessel occlusion were common in the young age group (29.7% versus 2.9% in dissection; 24.3% versus 8.7% in small vessel occlusion). Pneumonia was significantly high in the unfavorable outcome (mRS ≥2) group (p = 0.009).

Multivariable logistic regression identified age (OR = 1.06; 95% CI = 1.01−1.12) as a significant predictor of unfavorable outcome (mRS ≤ 1) at 1 year.

Conclusions: This retrospective study suggests that LMI at a young age shows a good clinical outcome. Age is a significant prognostic factor for good functional outcome after LMI, regardless of other demographical or clinical characteristics. Arterial dissection and SVO are frequent stroke mechanisms in the young age patients. Thus, young patients with LMI require a detailed diagnostic work up to examine such stroke mechanisms.

Keywords: Age, Lateral medullary infarction, Prognosis, Stroke mechanism

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CONTENTS

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INTRODUCTION

Lateral medullary infarction (LMI) is an alleged vascular syndrome developing in brainstem and is known to be caused by atherosclerosis in the vertebral artery (VA) or posterior inferior cerebellar artery (PICA) in 50% of the cases, by dissection in 15%, by small vessel occlusion in 13%, and by cardioembolism in 5%.[1] Clinical features such as sensory symptom, ataxia, dizziness and dysphagia according to neuroimaging characteristics of LMI have been investigated in detail, but the associated vasculopathies and clinical outcomes after LMI are rarely reported.[1-4] The prognosis for ischemic stroke in young adults is favorable; however, an early onset of stroke in young adults might indicate an underlying pathology or cause complications affecting their long-term prognosis.[5-9] While most studies report a favorable prognosis in LMI, only a few studies examine how non-atherosclerotic vasculopathy or the age of onset might affect neurological recovery and clinical complications.[1-5] In this study, I investigate the differences in vascular risk factors, etiologies, clinical outcomes, and prognoses between young and old patients with LMI.

MATERIALS AND METHODS

Study population

Patients were retrospectively recruited between February 1st, 2004 and January 31st, 2011 and followed up until August 31st, 2012. The patients were diagnosed with acute ischemic stroke involving lateral medullary lesion by brain MRI within seven days after symptom onset. Brain Magnetic Resonance Image (MRI)/Magnetic Resonance Angiography (MRA) was performed in all (n=106) patients and conventional angiography was performed to evaluate the dissection of VA or PICA in 38 patients with normal brain MRA.

Clinical information

Baseline characteristics included demographics such as age and gender, as well as conventional vascular risk factors, which were hypertension, diabetes mellitus, smoking history, hyperlipidemia, heart disease and previous history of stroke/TIA. Hypertension was defined as a history of antihypertensive treatment, systolic blood pressure $\geq$140 mmHg or diastolic blood pressure $\geq$ 90 mmHg.[14] Hyperlipidemia was defined as a history of anti-hyperlipidemia medication or a serum level of total cholesterol level > 240 mg/dL.[15] Diabetes mellitus was defined as a history of insulin or oral hypoglycemic treatment, HbA1c $\geq$ 6.5%; fasting blood glucose $\geq$126 mg/dL; or non-fasting blood glucose $\geq$ 200 mg/dL.[16]

Initially, all patients were evaluated with a neurological examination that determined the severity of the stroke based on the National Institute of Health Stroke Scale (NIHSS). The neurologists evaluated each patient's functional status every 3 months at an outpatient clinic. In case an evaluation could not be conducted at the clinic, then a trained nurse determined the patient's functional status through a structured telephone interview after 3 months and 1 year. This evaluation was performed as part of a program that monitored the quality of inpatient stroke care. The modified Rankin Scale score (mRS) and Barthel Index (BI) were used to determine a patient's functional outcome. I checked clinical events for 1 year after the occurrence of LMI; ischemic stroke, transient ischemic attack (TIA), myocardial infarction (MI), pneumonia, admission to intensive care unit (ICU) and death. Clinical ischemic stroke was defined as clinical findings consistent with stroke occurrence lasting ≥24 hours or lasting <24 hours, but with brain MRI evidence of acute ischemic stroke. TIA was defined as a clinical syndrome of acute loss of focal neurologic function of vascular origin with symptoms resolving with 24 hours. Death included any sudden death within 1 year after LMI, causes of which involved vascular or nonvascular events (underlying disease such as cancer, pneumonia and respiratory failure related death). I also checked dysphagia and sensory symptom after LMI for 1 year. Stroke subtypes were categorized according to the classification of the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria and arterial dissection alone: (1) large artery atherosclerosis (LAA); (2) small vessel occlusion(SVO): patients with hypertension, no cardioembolic source and normal angiography;

(3) cardioembolism; (4) VA or PICA dissection.[17] Patients participating in the study were divided into 2 groups based on their age. The young age group included patients between 18 and 59 years of age, while the old age group included patients over 60 years of age.18 I also divided the patients into 2 groups, with either favorable (mRS score, 0–1; BI, 95–100) or unfavorable (mRS score, 2–6; BI < 95) functional outcomes.[19]

Seoul National Bundang Hospital review board approved this study and specifically waived the need for consent.

Evaluation of LMI with Brain MRI and conventional angiography

I used brain MRI/MRA and conventional angiography to assess the lesion of LMI and the dissection of VA and PICA. Brain MRI/MRA was performed on a 1.5T or 3.0T superconducting magnet system. I defined VA or PICA dissections when the findings such as double lumen, intimal flap, string of pearls appearance, steno-occlusive and fusiform aneurysmal dilatation appeared in the brain MRI/MRA or in the conventional angiography.[10-13] Two neurologists retrospectively reviewed the brain MRI/MRA or the conventional angiographic findings and classified them.

Statistics

I used Student t-test for analysis of continuous data such as age and X2 test in order to analyze the categorized data. Multiple logistic regression analysis was performed to estimate the impact of the age, risk factors and stroke mechanisms on functional outcome. I calculated odds ratio (ORs) and their 95%

confidence intervals (CIs) of the favorable outcome to the unfavorable outcome. Adjustments were made with possible covariate factors such as age, vascular risk factors, clinical complication and stroke mechanisms which have been known to be associated with functional outcome from previous studies as well as those having a possible correlation with age in our data set. For all analyses, a 2-tailed $P<0.05$ was considered statistically significant. All statistical analyses were performed with the SPSS program (Version 18.0).

RESULTS

Baseline characteristics

A total of 106 patients with acute LMI were selected for the study. The mean age for all patients was 61.5 ± 12 years (range, 30–90 years), which included 76 (71.7%) men and 30 women. The demographics, risk factors, and stroke subtypes for the 106 patients are summarized based on the age group in Table 1. There were 37 patients (31 men and 6 women) in the young age group (18–59 years) and 69 patients (45 men and 24 women) in the old age group (≥60 years). The mean age was 48.3 ± 8.0 years for the young age group and 68.5 ± 7.05 years for the old age group. The vascular risk factors diabetes mellitus (p = 0.049) and hypertension (p= 0.014) were more prevalent in the old age group. There were no significant differences between groups for smoking, hyperlipidemia, ischemic events, coronary heart disease, or previous mRS. Initial median NIHSS was 2 (interquartile range, 1–4) and was not significantly different between groups at the initial assessment (p = 0.996) (Table 1).

As indicated in Table 1, LAA (n = 69, 65.1%) was the prevalent mechanism in both groups with more/greater prevalence in the old age group. Arterial dissection and SVO were more common in the young age group than in the old age group (n = 11, 29.7% vs. n = 2, 2.9% in dissection; n = 9, 24.3% vs. n = 6, 8.7% in SVO, p < 0.001) (Table 1). Of the 13 arterial dissections, 10 patients had VA dissection (8 in young age group; 2 in old age group) and 3 were PICA dissection (in only young age group).

Table 1 Baseline differences in young and older patients with LMI

	All patients (n = 106)	**Young age (<60 Years) (n = 37)**	**Old age (≥60 years) (n = 69)**	**P value**
Age, mean (SD), y	61.5 (12.2)	48.3 (8.0)	68.5 (7.1)	<0.001*
Male, n (%)	76 (71.7)	31 (83.8)	45 (65.2)	0.069†
Risk Factor, n (%)				
Diabetes Mellitus	34 (32.1)	7 (18.9)	27 (39.1)	0.049†
Hypertension	53 (50)	12 (32.4)	41 (59.4)	0.014†
Previous TIA or Stroke	9 (8.5)	1 (2.7)	8 (11.6)	0.111†
Hyperlipidemia	12 (11.3)	2 (5.4)	10 (14.5)	0.209†
Coronary Heart disease	8 (7.5)	1 (2.7)	7 (10.1)	0.167†
Smoking	37 (34.9)	17 (45.9)	20 (29)	0.091†
Previous mRS, n (%)				0.182†
0	101 (95.3)	36 (97.3)	65 (94.2)	
1	2 (1.9)	1 (2.7)	1 (1.4)	
2	2 (1.9)	0	2 (2.9)	
3	1 (0.9)	0	1 (1.4)	
Initial NIHSS, median (IQR)	2 (1−4)	1 (1−4)	2 (1−4)	0.996 †

Stroke Subtype, n (%)				<0.001†
SVO	15 (14.2)	9 (24.3)	6 (8.7)	
LAA	69 (65.1)	17 (45.9)	52 (75.4)	
CE	9 (8.5)	0	9 (13.0)	
Arterial Dissection	13 (12.3)	11 (29.7)	2 (2.9)	
VA	10 (9.4)	8 (21.6)	2 (2.9)	
PICA	3 (2.8)	3 (8.1)		
LMI lesion				0.975†
Pure LMI	74 (69.8)	26 (70.3)	48 (69.6)	
LMI and cerebellum	24 (22.6)	8 (21.6)	16 (23.2)	
LMI and others	8 (7.5)	3 (8.1)	5 (7.2)	

LMI and others: Lateral medullary infarction and cerebral or brainstem lesions

*P value by Student's t- test

† P value by Chi-square test

Clinical outcomes at 1 year

Patients who showed a favorable outcome (mRS score 0–1) were significantly younger than those who showed an unfavorable outcome (p = 0.001). The prevalence of hypertension and coronary heart disease was higher in the unfavorable outcome group than in the favorable outcome group (HTN, p = 0.049; coronary heart disease, p = 0.016) (Table 2). Initial NIHSS score was not different between the favorable and unfavorable outcome groups. For stroke subtypes, SVO was more prevalent in the favorable outcome group, but CE was more prevalent in the unfavorable outcome patients (p = 0.011). The prevalence of arterial dissection was similar in both groups.

There were no significant differences in 3 month mRS and BI between the young and old age groups (p = 0.997, p = 0.141) (Table 3). The medians for mRS and BI at 1 year were not different between the 2 groups (mRS, 1 [0–1] versus 1 [0–3], p = 0.159; BI, 100 [100–100] versus 100 [100–100], p = 0.245). The young age group showed a higher percentage of favorable outcomes (mRS, 0–1; BI, 95–100) at 1 year compared to the old age group (mRS, 31 [83.8%] vs. 40 (58%), p = 0.007; BI, 35 [94.6%] vs. 55 (79.7%), p = 0.041) (Table 3), and no patient in the young age group showed a poor prognosis (mRS $\geq$ 4). Moreover, older patients showed an unfavorable prognosis at 1 year (OR 1.07, CI [1.02−1.11]) (Table 4). There were no significant differences between the young and old age groups in the infarction locations, as indicated by brain MRI (Table 1).

Patients' follow-ups occurred over a median of 4.65 years (IQR, 3.25–6.00

years). Clinical events were observed in 9 patients in the first year following the LMI, which included 5 stroke/TIA cases (4.7%) and 4 medical-related deaths (3.8%) (septic shock, gastric cancer, hematologic cancer). No death occurred in the young age group. Stroke/TIA occurred more frequently in the old age group (n = 1, 2.7% vs. n = 4, 5.8%), but this difference was insignificant (p = 0.474). Older patients were more frequently presented with aspiration pneumonia, and all 5 patients were treated in the ICU. Dysphagia-related aspiration pneumonia was not significantly different between the groups (Table 3).

The results of the logistic regression analyses were analyzed separately for mRS at 1 year. The younger age was an independent predictive variable of a good clinical outcome in LMI (Table 4).

Table 2 Clinical features observed at the 1 year evaluation.

	All patients (n = 106)	**Favorable (mRS 0–1) (n = 71)**	**Unfavorable (mRS ≥ 2) (n = 35)**	**P value**
Age, mean (SD), y	61.5 (12.2)	58.8 (11.0)	66.9 (10.9)	0.001*
Male, n (%)	76 (71.7)	55 (77.5)	21 (60.0)	0.051†
Risk Factor, n (%)				
Diabetes Mellitus	34 (32.1)	23 (32.4)	11 (31.4)	0.552†
Hypertension	53 (50)	31 (43.7)	22 (62.9)	0.049†
Previous TIA or Stroke	9 (8.5)	4 (5.6)	5 (14.3)	0.130†
Hyperlipidemia	12 (11.3)	7 (9.9)	5 (14.3)	0.354†
Coronary heart disease	8 (7.5)	1 (2.7)	7 (10.1)	0.016†
Smoking	37 (34.9)	28 (39.4)	9 (25.7)	0.119†
Previous mRS, n (%)				0.350†
0	101 (95.3)	68 (95.8)	33 (94.3)	
1	2 (1.9)	2 (2.8)	0	
2	2 (1.9)	1 (1.4)	1 (2.9)	
3	1 (0.9)	0	1 (2.9)	

Initial NIHSS, median (IQR)	2 (1–4)	2 (1–3)	3 (1–4)	0.179†
Stroke Subtype, n (%)				0.011†
SVO	15 (14.2)	13 (18.3)	2 (5.7)	
LAA	69 (65.1)	48 (67.6)	21 (60.0)	
CE	9 (8.5)	2 (2.8)	7 (20.0)	
Arterial Dissection	13 (12.3)	8 (11.3)	5 (14.3)	
VA	10 (9.4)	6 (8.5)	4 (11.4)	
PICA	3 (2.8)	2 (2.8)	1 (2.9)	
LMI lesion				0.545†
Pure LMI	74 (69.8)	50 (70.4)	24 (68.6)	
LMI and cerebellum	24 (22.6)	17 (23.9)	7 (20.0)	
LMI and others	8 (7.5)	4 (5.6)	4 (11.4)	
Complication, 1Y, n (%)				
Dysphagia	37 (34.9)	22 (31)	15 (42.9)	0.228†
Pneumonia	10 (9.4)	3 (4.2)	7 (20)	0.009†
ICU care	5 (4.7)	0	5 (14.3)	0.001†

LMI and others: Lateral medullary infarction and cerebral or brainstem lesions

*P value by Student *t* test †P value by Chi-square test

Table 3 Clinical outcomes during 1 Year

	All patients (n = 106)	Young age (<60 years) (n = 37)	Old age (≥60 years) (n = 69)	P value†
mRS at 3 Months				0.997
mRS 0–1	63 (59.4)	22 (59.5)	41 (59.4)	
mRS ≥2	43 (40.6)	15 (40.5)	28 (40.6)	
mRS at 1 Year				0.007
mRS 0–1	71 (67)	31 (83.8)	40 (58)	
mRS ≥2	35 (33)	6 (16.2)	29 (42)	
BI at 3 Months				0.141
BI (95–100)	90 (84.9)	31 (91.9)	56 (81.2)	
BI (<95)	16 (15.1)	3 (8.1)	13 (18.8)	
BI at 1 Year				0.041
BI (95–100)	90 (84.9)	35 (94.6)	55 (79.7)	
BI (<95)	16 (15.1)	2 (5.4)	14 (20.3)	
Clinical Event, 1Y				
n (%)				
Mortality	4 (3.8)	0	4 (5.8)	0.135†

Stroke/TIA	5 (4.7)	1 (2.7)	4 (5.8)	0.474†
Complication, 1Y				
n (%)				
Dysphagia	37 (34.9)	15 (40.5)	22 (31.9)	0.373†
Pneumonia	10 (9.4)	1 (2.7)	9 (13.0)	0.083†
ICU care	5 (4.7)	0 (0)	5 (7.2)	0.093†

mRS, Modified Rankin Score; BI, Barthel Index; TIA, Transient Ischemic Attack; MI, Myocardial Infarction

†P value by Chi-square test

Table 4. Multiple logistic regression analysis for a favorable outcome at 1 year

Outcome	**Unadjusted**		**Adjusted**		
Predictor	**OR**	**95% CI**	**OR**	**95% CI**	**P value**
Age	1.07	1.02–1.11	1.06	1.01–1.12	0.026
Diabetes Mellitus	0.96	0.40–2.28	0.90	0.30–2.64	0.116
Hypertension	2.18	0.95–5.01	2.30	0.82–6.50	0.841
Pneumonia	5.67	1.37–23.50	3.429	0.70–16.77	0.128
Stroke Subtype					0.056
SVO	1		1		
LAA	2.84	0.59–13.73	1.67	0.30–9.46	
CE	22.75	2.61–198.19	7.83	0.75–82.00	
Arterial Dissection	4.06	0.63–26.13	9.00	1.10–73.86	

DISCUSSION

In the present study, I examined the outcomes of 106 patients with LMI. I found that a young age was the best predictor for a good clinical outcome at 1 year following an LMI and observed that LAA was the most common etiological mechanism in both young and old age groups as VA or PICA dissections were confirmed in 12.3% of all patients. This distribution of stroke mechanism is similar to what was observed in a previous study.[1] Further, similar to previous studies, diabetes mellitus and hypertension were the most common vascular risk factors found in older patients.[5-7, 20-22] Hyperlipidemia, history of previous stroke, and coronary heart disease were common in the old age group, but these findings were not statistically significant differed from the results of other studies.[5-7, 20-22]

The functional outcome of young patients who survived stroke was often favorable.[5-7, 20-22] For the LMI patients examined in our study, favorable outcome was confirmed in 60% of patients at 3 months and in 67% at 1 year. Regarding the prognosis according to ages, younger patients more often showed a favorable outcome at 1 year (mRS $\leq$ 1, 83.8%), and therefore, showed an improved prognosis compared to older patients. Similar to the findings of previous studies,[1-5] younger patients were often functionally independent at 1 year, and none of the younger patients showed grave outcomes (mRS $\geq$ 4). Young patients also showed better BI scores at 1 year than older patients (94.6% vs. 79.7%) while displaying great recovery ability after ischemic stroke. In experimental studies, aged rats showed a premature

formation of scar and delayed neuron regenerative capacity in brain due to impaired glial repairing, angiogenesis and neuronal regulation.[22-24] These results might reflect the age effect of vascular risk factors since hypertension and diabetes mellitus are common in old age. The incidence of clinical events was not statistically different between young and old patients; however, they were more prevalent in older patients. Of the 9 clinical events observed at 1 year, only 1 (2.7%) stroke/TIA occurred in the young age group, while 4 (5.8%) stroke/TIA cases and all 4 deaths (5.8%) occurred in the old group. The frequency of dysphagia was not significantly different between the groups, but aspiration pneumonia and ICU care occurred more frequently in the older group. These results were associated with an improved recovery at a young age.[20-22] The incidence of pneumonia with dysphagia that was observed in the present study was lower than what was reported in previous studies.[1,4,25,26,29] I suspect this reduction in pneumonia complication was related to an increase and development in stroke unit and ICU care.[27]

Arterial dissection is a prominent etiological mechanism in LMI and occurred more often in younger patients.[1,4] Brain MRA is a reliable, noninvasive method of diagnosing extracranial internal carotid artery dissection, but conventional angiography remains useful in vertebral artery dissection.28 Thus, young patients with LMI require a detailed diagnostic work up to examine such stroke mechanisms.

The present study has some limitations. First, since this is a retrospective study, there is a possibility of selection bias; therefore, our reviewing data such as demographic, epidemiologic and clinical data had some limitations.

Second, this is a small population study, despite the fact that our study population is larger than that of previous studies of LMI. Thus, demonstrating statistical significance may be difficult. Larger multicenter studies with an adequate population size are necessary to elucidate the prognosis or etiological mechanisms for patients suffering from LMI.

CONCLUSION

This retrospective study revealed different stroke mechanisms and favorable outcomes in young patients with LMI. The young patients showed less frequent medical complications. Age is a significant prognostic factor for good functional outcome after LMI, regardless of other demographical or clinical characteristics. The arterial dissection was more frequent in young patients, so it is reasonable to evaluate VA or PICA by conventional angiography combined with MR angiography in young age patients with LMI.

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국문 초록

서론: 이전에 외측 연수 경색에서 젊은 환자와 노령 환자의 뇌졸중 발생 기전과 예후에 관련된 연구는 많지 않았다. 이에 본 연구에서는 외측 연수 경색 환자에서 연령에 따른 위험인자, 원인 및 예후의 차이점을 조사 하였다.

방법: 2004 년 2 월부터 2011 년 1 월까지 증상 발생 7 일 이내에 입원한 외측 연수 경색 환자들의 기록을 후향적으로 검토 및 조사를 하였다. 증상 발생 1 년간 신경학적인 결과를 바델 지수와 변형랜킨척도를 이용하여 평가 하였다. 또한 증상 발생 1 년간의 임상 사례를 확인하였다. 환자는 연령에 따라 두 그룹: 18-59 세(젊은 연령), 60 세 이상(노령)으로 나누었다. 또한 환자는 신경학적인 결과에 따라 좋은 예후(변형랜킨척도 0-1, 바델지수 95-100) 그룹과 나쁜 예후(변형랜킨척도 2-6, 바델지수<95) 그룹으로 나누었다. 환자들은 혈관 병변을 평가하지 위하여 뇌 자이 공명 혈관 조영검사와 혈관 조영술을 시행하였다.

결과: 본 연구에서는 총 106 명의 환자가 포함되었고 이 중 젊은 연령 그룹에는 37 명의 환자, 노령 그룹에는 69 명의 환자가 속하게 되었다. 본 연구에서 가장 흔한 뇌경색 기전은 양 그룹 모두에서 큰 동맥 죽상 경화증이(젊은 연령 그룹 45.9%, 노령 그룹 75.4%) 관찰되었다. 동맥 박리와 소혈관 폐색은 젊은 연령 그룹에서 많이

발생하였다. (동맥 박리 29.7% 대 2.9%, 소혈관 폐색 24.3% 대 8.7%) 폐렴은 나쁜 예후 그룹 (변형랜킨척도 ≥2) 에서 유의하게 많이 발생하였다. 다변량 로지스틱 회귀분석을 통하여 연령이 1 년의 나쁜 예후에 중요한 예측 인자인 것으로 확인하였다.

결론: 본 후향적인 연구는 젊은 연령의 외측 연수 경색 환자들이 좋은 예후와 결과를 보이는 것을 확인하였다. 젊은 연령 임상양상이나 여러 요인들의 효과에 독립적으로 외측 연수 경색 이후에 좋은 기능적인 예후의 예측인자일 수 있다. 동맥 박리와 소혈관 폐색은 젊은 연령 환자에서 중요한 뇌졸중 메커니즘이다. 따라서 젊은 외측 연수 경색 환자들은 뇌졸중 메커니즘을 확인하기 위해 자세한 진단 평가가 필요하다.

주요어 : 연령, 외측 연수 경색, 예후, 뇌졸중 메커니즘

학 번 : 2012-21740

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One-Year Prognosis and Outcome according to Age with Lateral Medullary Infarction

외측 연수 경색에서 연령에 따른 1 년의 예후 및 결과

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A thesis of the Degree of Master of Medicine

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One-Year Prognosis and Outcome according to Age with Lateral Medullary Infarction

by
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ABSTRACT

Introduction: Few studies have compared stroke mechanisms and prognosis in lateral medullary infarction (LMI) between young and old patients. Here, I investigated the differences in the risk factors, etiologies, and prognosis between young and old patients with LMI.

Materials and Methods: I reviewed retrospectively consecutive patients with acute LMI who were admitted within 7 days after symptom onset between February 2004 and January 2011. Neurological outcomes I measured by Barthel Index (BI) and Modified Rankin Scale (mRS) at 1 year, and clinical events were checked for 1 year. Patients were divided into two groups according to their age: 18-59 years (young age group), and over 60 years (old age group). I also divided the patients into two groups with favorable outcome (mRS score 0-1 and BI 95-100) and unfavorable outcome (mRS score ≥2 and BI <95). I performed Brain MR angiography (MRA) or conventional angiography to evaluate vascular pathologies.

Results: A total of 106 patients were included in the study, of whom 37 were considered young patients (age, 18–59 years) and 69 were considered old patients (age, 60≥ years). The most common etiologic mechanism observed in this study was large artery atherosclerosis, which was observed in both groups (young group, 45.9%; old group, 75.4%). Arterial dissection and small vessel occlusion were common in the young age group (29.7% versus 2.9% in dissection; 24.3% versus 8.7% in small vessel occlusion). Pneumonia was significantly high in the unfavorable outcome (mRS ≥2) group (p = 0.009).

Multivariable logistic regression identified age (OR = 1.06; 95% CI = 1.01−1.12) as a significant predictor of unfavorable outcome (mRS ≤ 1) at 1 year.

Conclusions: This retrospective study suggests that LMI at a young age shows a good clinical outcome. Age is a significant prognostic factor for good functional outcome after LMI, regardless of other demographical or clinical characteristics. Arterial dissection and SVO are frequent stroke mechanisms in the young age patients. Thus, young patients with LMI require a detailed diagnostic work up to examine such stroke mechanisms.

Keywords: Age, Lateral medullary infarction, Prognosis, Stroke mechanism

Student number: 2012-21740

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INTRODUCTION

Lateral medullary infarction (LMI) is an alleged vascular syndrome developing in brainstem and is known to be caused by atherosclerosis in the vertebral artery (VA) or posterior inferior cerebellar artery (PICA) in 50% of the cases, by dissection in 15%, by small vessel occlusion in 13%, and by cardioembolism in 5%.[1] Clinical features such as sensory symptom, ataxia, dizziness and dysphagia according to neuroimaging characteristics of LMI have been investigated in detail, but the associated vasculopathies and clinical outcomes after LMI are rarely reported.[1-4] The prognosis for ischemic stroke in young adults is favorable; however, an early onset of stroke in young adults might indicate an underlying pathology or cause complications affecting their long-term prognosis.[5-9] While most studies report a favorable prognosis in LMI, only a few studies examine how non-atherosclerotic vasculopathy or the age of onset might affect neurological recovery and clinical complications.[1-5] In this study, I investigate the differences in vascular risk factors, etiologies, clinical outcomes, and prognoses between young and old patients with LMI.

MATERIALS AND METHODS

Study population

Patients were retrospectively recruited between February 1st, 2004 and January 31st, 2011 and followed up until August 31st, 2012. The patients were diagnosed with acute ischemic stroke involving lateral medullary lesion by brain MRI within seven days after symptom onset. Brain Magnetic Resonance Image (MRI)/Magnetic Resonance Angiography (MRA) was performed in all (n=106) patients and conventional angiography was performed to evaluate the dissection of VA or PICA in 38 patients with normal brain MRA.

Clinical information

Baseline characteristics included demographics such as age and gender, as well as conventional vascular risk factors, which were hypertension, diabetes mellitus, smoking history, hyperlipidemia, heart disease and previous history of stroke/TIA. Hypertension was defined as a history of antihypertensive treatment, systolic blood pressure $\geq$140 mmHg or diastolic blood pressure $\geq$ 90 mmHg.[14] Hyperlipidemia was defined as a history of anti-hyperlipidemia medication or a serum level of total cholesterol level > 240 mg/dL.[15] Diabetes mellitus was defined as a history of insulin or oral hypoglycemic treatment, HbA1c $\geq$ 6.5%; fasting blood glucose $\geq$126 mg/dL; or non-fasting blood glucose $\geq$ 200 mg/dL.[16]

Initially, all patients were evaluated with a neurological examination that determined the severity of the stroke based on the National Institute of Health Stroke Scale (NIHSS). The neurologists evaluated each patient's functional status every 3 months at an outpatient clinic. In case an evaluation could not be conducted at the clinic, then a trained nurse determined the patient's functional status through a structured telephone interview after 3 months and 1 year. This evaluation was performed as part of a program that monitored the quality of inpatient stroke care. The modified Rankin Scale score (mRS) and Barthel Index (BI) were used to determine a patient's functional outcome. I checked clinical events for 1 year after the occurrence of LMI; ischemic stroke, transient ischemic attack (TIA), myocardial infarction (MI), pneumonia, admission to intensive care unit (ICU) and death. Clinical ischemic stroke was defined as clinical findings consistent with stroke occurrence lasting ≥24 hours or lasting <24 hours, but with brain MRI evidence of acute ischemic stroke. TIA was defined as a clinical syndrome of acute loss of focal neurologic function of vascular origin with symptoms resolving with 24 hours. Death included any sudden death within 1 year after LMI, causes of which involved vascular or nonvascular events (underlying disease such as cancer, pneumonia and respiratory failure related death). I also checked dysphagia and sensory symptom after LMI for 1 year. Stroke subtypes were categorized according to the classification of the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria and arterial dissection alone: (1) large artery atherosclerosis (LAA); (2) small vessel occlusion(SVO): patients with hypertension, no cardioembolic source and normal angiography;

(3) cardioembolism; (4) VA or PICA dissection.[17] Patients participating in the study were divided into 2 groups based on their age. The young age group included patients between 18 and 59 years of age, while the old age group included patients over 60 years of age.18 I also divided the patients into 2 groups, with either favorable (mRS score, 0–1; BI, 95–100) or unfavorable (mRS score, 2–6; BI < 95) functional outcomes.[19]

Seoul National Bundang Hospital review board approved this study and specifically waived the need for consent.

Evaluation of LMI with Brain MRI and conventional angiography

I used brain MRI/MRA and conventional angiography to assess the lesion of LMI and the dissection of VA and PICA. Brain MRI/MRA was performed on a 1.5T or 3.0T superconducting magnet system. I defined VA or PICA dissections when the findings such as double lumen, intimal flap, string of pearls appearance, steno-occlusive and fusiform aneurysmal dilatation appeared in the brain MRI/MRA or in the conventional angiography.[10-13] Two neurologists retrospectively reviewed the brain MRI/MRA or the conventional angiographic findings and classified them.

Statistics

I used Student t-test for analysis of continuous data such as age and X2 test in order to analyze the categorized data. Multiple logistic regression analysis was performed to estimate the impact of the age, risk factors and stroke mechanisms on functional outcome. I calculated odds ratio (ORs) and their 95%

confidence intervals (CIs) of the favorable outcome to the unfavorable outcome. Adjustments were made with possible covariate factors such as age, vascular risk factors, clinical complication and stroke mechanisms which have been known to be associated with functional outcome from previous studies as well as those having a possible correlation with age in our data set. For all analyses, a 2-tailed $P<0.05$ was considered statistically significant. All statistical analyses were performed with the SPSS program (Version 18.0).

RESULTS

Baseline characteristics

A total of 106 patients with acute LMI were selected for the study. The mean age for all patients was 61.5 ± 12 years (range, 30–90 years), which included 76 (71.7%) men and 30 women. The demographics, risk factors, and stroke subtypes for the 106 patients are summarized based on the age group in Table 1. There were 37 patients (31 men and 6 women) in the young age group (18–59 years) and 69 patients (45 men and 24 women) in the old age group (≥60 years). The mean age was 48.3 ± 8.0 years for the young age group and 68.5 ± 7.05 years for the old age group. The vascular risk factors diabetes mellitus (p = 0.049) and hypertension (p= 0.014) were more prevalent in the old age group. There were no significant differences between groups for smoking, hyperlipidemia, ischemic events, coronary heart disease, or previous mRS. Initial median NIHSS was 2 (interquartile range, 1–4) and was not significantly different between groups at the initial assessment (p = 0.996) (Table 1).

As indicated in Table 1, LAA (n = 69, 65.1%) was the prevalent mechanism in both groups with more/greater prevalence in the old age group. Arterial dissection and SVO were more common in the young age group than in the old age group (n = 11, 29.7% vs. n = 2, 2.9% in dissection; n = 9, 24.3% vs. n = 6, 8.7% in SVO, p < 0.001) (Table 1). Of the 13 arterial dissections, 10 patients had VA dissection (8 in young age group; 2 in old age group) and 3 were PICA dissection (in only young age group).

Table 1 Baseline differences in young and older patients with LMI

	All patients (n = 106)	**Young age (<60 Years) (n = 37)**	**Old age (≥60 years) (n = 69)**	**P value**
Age, mean (SD), y	61.5 (12.2)	48.3 (8.0)	68.5 (7.1)	<0.001*
Male, n (%)	76 (71.7)	31 (83.8)	45 (65.2)	0.069†
Risk Factor, n (%)				
Diabetes Mellitus	34 (32.1)	7 (18.9)	27 (39.1)	0.049†
Hypertension	53 (50)	12 (32.4)	41 (59.4)	0.014†
Previous TIA or Stroke	9 (8.5)	1 (2.7)	8 (11.6)	0.111†
Hyperlipidemia	12 (11.3)	2 (5.4)	10 (14.5)	0.209†
Coronary Heart disease	8 (7.5)	1 (2.7)	7 (10.1)	0.167†
Smoking	37 (34.9)	17 (45.9)	20 (29)	0.091†
Previous mRS, n (%)				0.182†
0	101 (95.3)	36 (97.3)	65 (94.2)	
1	2 (1.9)	1 (2.7)	1 (1.4)	
2	2 (1.9)	0	2 (2.9)	
3	1 (0.9)	0	1 (1.4)	
Initial NIHSS, median (IQR)	2 (1−4)	1 (1−4)	2 (1−4)	0.996 †

Stroke Subtype, n (%)				<0.001†
SVO	15 (14.2)	9 (24.3)	6 (8.7)	
LAA	69 (65.1)	17 (45.9)	52 (75.4)	
CE	9 (8.5)	0	9 (13.0)	
Arterial Dissection	13 (12.3)	11 (29.7)	2 (2.9)	
VA	10 (9.4)	8 (21.6)	2 (2.9)	
PICA	3 (2.8)	3 (8.1)		
LMI lesion				0.975†
Pure LMI	74 (69.8)	26 (70.3)	48 (69.6)	
LMI and cerebellum	24 (22.6)	8 (21.6)	16 (23.2)	
LMI and others	8 (7.5)	3 (8.1)	5 (7.2)	

LMI and others: Lateral medullary infarction and cerebral or brainstem lesions

*P value by Student's t- test

† P value by Chi-square test

Clinical outcomes at 1 year

Patients who showed a favorable outcome (mRS score 0–1) were significantly younger than those who showed an unfavorable outcome (p = 0.001). The prevalence of hypertension and coronary heart disease was higher in the unfavorable outcome group than in the favorable outcome group (HTN, p = 0.049; coronary heart disease, p = 0.016) (Table 2). Initial NIHSS score was not different between the favorable and unfavorable outcome groups. For stroke subtypes, SVO was more prevalent in the favorable outcome group, but CE was more prevalent in the unfavorable outcome patients (p = 0.011). The prevalence of arterial dissection was similar in both groups.

There were no significant differences in 3 month mRS and BI between the young and old age groups (p = 0.997, p = 0.141) (Table 3). The medians for mRS and BI at 1 year were not different between the 2 groups (mRS, 1 [0–1] versus 1 [0–3], p = 0.159; BI, 100 [100–100] versus 100 [100–100], p = 0.245). The young age group showed a higher percentage of favorable outcomes (mRS, 0–1; BI, 95–100) at 1 year compared to the old age group (mRS, 31 [83.8%] vs. 40 (58%), p = 0.007; BI, 35 [94.6%] vs. 55 (79.7%), p = 0.041) (Table 3), and no patient in the young age group showed a poor prognosis (mRS $\geq$ 4). Moreover, older patients showed an unfavorable prognosis at 1 year (OR 1.07, CI [1.02−1.11]) (Table 4). There were no significant differences between the young and old age groups in the infarction locations, as indicated by brain MRI (Table 1).

Patients' follow-ups occurred over a median of 4.65 years (IQR, 3.25–6.00

years). Clinical events were observed in 9 patients in the first year following the LMI, which included 5 stroke/TIA cases (4.7%) and 4 medical-related deaths (3.8%) (septic shock, gastric cancer, hematologic cancer). No death occurred in the young age group. Stroke/TIA occurred more frequently in the old age group (n = 1, 2.7% vs. n = 4, 5.8%), but this difference was insignificant (p = 0.474). Older patients were more frequently presented with aspiration pneumonia, and all 5 patients were treated in the ICU. Dysphagia-related aspiration pneumonia was not significantly different between the groups (Table 3).

The results of the logistic regression analyses were analyzed separately for mRS at 1 year. The younger age was an independent predictive variable of a good clinical outcome in LMI (Table 4).

Table 2 Clinical features observed at the 1 year evaluation.

	All patients (n = 106)	**Favorable (mRS 0–1) (n = 71)**	**Unfavorable (mRS ≥ 2) (n = 35)**	**P value**
Age, mean (SD), y	61.5 (12.2)	58.8 (11.0)	66.9 (10.9)	0.001*
Male, n (%)	76 (71.7)	55 (77.5)	21 (60.0)	0.051†
Risk Factor, n (%)				
Diabetes Mellitus	34 (32.1)	23 (32.4)	11 (31.4)	0.552†
Hypertension	53 (50)	31 (43.7)	22 (62.9)	0.049†
Previous TIA or Stroke	9 (8.5)	4 (5.6)	5 (14.3)	0.130†
Hyperlipidemia	12 (11.3)	7 (9.9)	5 (14.3)	0.354†
Coronary heart disease	8 (7.5)	1 (2.7)	7 (10.1)	0.016†
Smoking	37 (34.9)	28 (39.4)	9 (25.7)	0.119†
Previous mRS, n (%)				0.350†
0	101 (95.3)	68 (95.8)	33 (94.3)	
1	2 (1.9)	2 (2.8)	0	
2	2 (1.9)	1 (1.4)	1 (2.9)	
3	1 (0.9)	0	1 (2.9)	

Initial NIHSS, median (IQR)	2 (1–4)	2 (1–3)	3 (1–4)	0.179†
Stroke Subtype, n (%)				0.011†
SVO	15 (14.2)	13 (18.3)	2 (5.7)	
LAA	69 (65.1)	48 (67.6)	21 (60.0)	
CE	9 (8.5)	2 (2.8)	7 (20.0)	
Arterial Dissection	13 (12.3)	8 (11.3)	5 (14.3)	
VA	10 (9.4)	6 (8.5)	4 (11.4)	
PICA	3 (2.8)	2 (2.8)	1 (2.9)	
LMI lesion				0.545†
Pure LMI	74 (69.8)	50 (70.4)	24 (68.6)	
LMI and cerebellum	24 (22.6)	17 (23.9)	7 (20.0)	
LMI and others	8 (7.5)	4 (5.6)	4 (11.4)	
Complication, 1Y, n (%)				
Dysphagia	37 (34.9)	22 (31)	15 (42.9)	0.228†
Pneumonia	10 (9.4)	3 (4.2)	7 (20)	0.009†
ICU care	5 (4.7)	0	5 (14.3)	0.001†

LMI and others: Lateral medullary infarction and cerebral or brainstem lesions

*P value by Student *t* test †P value by Chi-square test

Table 3 Clinical outcomes during 1 Year

	All patients (n = 106)	Young age (<60 years) (n = 37)	Old age (≥60 years) (n = 69)	P value†
mRS at 3 Months				0.997
mRS 0–1	63 (59.4)	22 (59.5)	41 (59.4)	
mRS ≥2	43 (40.6)	15 (40.5)	28 (40.6)	
mRS at 1 Year				0.007
mRS 0–1	71 (67)	31 (83.8)	40 (58)	
mRS ≥2	35 (33)	6 (16.2)	29 (42)	
BI at 3 Months				0.141
BI (95–100)	90 (84.9)	31 (91.9)	56 (81.2)	
BI (<95)	16 (15.1)	3 (8.1)	13 (18.8)	
BI at 1 Year				0.041
BI (95–100)	90 (84.9)	35 (94.6)	55 (79.7)	
BI (<95)	16 (15.1)	2 (5.4)	14 (20.3)	
Clinical Event, 1Y				
n (%)				
Mortality	4 (3.8)	0	4 (5.8)	0.135†

Stroke/TIA	5 (4.7)	1 (2.7)	4 (5.8)	0.474†
Complication, 1Y				
n (%)				
Dysphagia	37 (34.9)	15 (40.5)	22 (31.9)	0.373†
Pneumonia	10 (9.4)	1 (2.7)	9 (13.0)	0.083†
ICU care	5 (4.7)	0 (0)	5 (7.2)	0.093†

mRS, Modified Rankin Score; BI, Barthel Index; TIA, Transient Ischemic Attack; MI, Myocardial Infarction

†P value by Chi-square test

Table 4. Multiple logistic regression analysis for a favorable outcome at 1 year

Outcome	**Unadjusted**		**Adjusted**		
Predictor	**OR**	**95% CI**	**OR**	**95% CI**	**P value**
Age	1.07	1.02–1.11	1.06	1.01–1.12	0.026
Diabetes Mellitus	0.96	0.40–2.28	0.90	0.30–2.64	0.116
Hypertension	2.18	0.95–5.01	2.30	0.82–6.50	0.841
Pneumonia	5.67	1.37–23.50	3.429	0.70–16.77	0.128
Stroke Subtype					0.056
SVO	1		1		
LAA	2.84	0.59–13.73	1.67	0.30–9.46	
CE	22.75	2.61–198.19	7.83	0.75–82.00	
Arterial Dissection	4.06	0.63–26.13	9.00	1.10–73.86	

DISCUSSION

In the present study, I examined the outcomes of 106 patients with LMI. I found that a young age was the best predictor for a good clinical outcome at 1 year following an LMI and observed that LAA was the most common etiological mechanism in both young and old age groups as VA or PICA dissections were confirmed in 12.3% of all patients. This distribution of stroke mechanism is similar to what was observed in a previous study.[1] Further, similar to previous studies, diabetes mellitus and hypertension were the most common vascular risk factors found in older patients.[5-7, 20-22] Hyperlipidemia, history of previous stroke, and coronary heart disease were common in the old age group, but these findings were not statistically significant differed from the results of other studies.[5-7, 20-22]

The functional outcome of young patients who survived stroke was often favorable.[5-7, 20-22] For the LMI patients examined in our study, favorable outcome was confirmed in 60% of patients at 3 months and in 67% at 1 year. Regarding the prognosis according to ages, younger patients more often showed a favorable outcome at 1 year (mRS $\leq$ 1, 83.8%), and therefore, showed an improved prognosis compared to older patients. Similar to the findings of previous studies,[1-5] younger patients were often functionally independent at 1 year, and none of the younger patients showed grave outcomes (mRS $\geq$ 4). Young patients also showed better BI scores at 1 year than older patients (94.6% vs. 79.7%) while displaying great recovery ability after ischemic stroke. In experimental studies, aged rats showed a premature

formation of scar and delayed neuron regenerative capacity in brain due to impaired glial repairing, angiogenesis and neuronal regulation.[22-24] These results might reflect the age effect of vascular risk factors since hypertension and diabetes mellitus are common in old age. The incidence of clinical events was not statistically different between young and old patients; however, they were more prevalent in older patients. Of the 9 clinical events observed at 1 year, only 1 (2.7%) stroke/TIA occurred in the young age group, while 4 (5.8%) stroke/TIA cases and all 4 deaths (5.8%) occurred in the old group. The frequency of dysphagia was not significantly different between the groups, but aspiration pneumonia and ICU care occurred more frequently in the older group. These results were associated with an improved recovery at a young age.[20-22] The incidence of pneumonia with dysphagia that was observed in the present study was lower than what was reported in previous studies.[1,4,25,26,29] I suspect this reduction in pneumonia complication was related to an increase and development in stroke unit and ICU care.[27]

Arterial dissection is a prominent etiological mechanism in LMI and occurred more often in younger patients.[1,4] Brain MRA is a reliable, noninvasive method of diagnosing extracranial internal carotid artery dissection, but conventional angiography remains useful in vertebral artery dissection.28 Thus, young patients with LMI require a detailed diagnostic work up to examine such stroke mechanisms.

The present study has some limitations. First, since this is a retrospective study, there is a possibility of selection bias; therefore, our reviewing data such as demographic, epidemiologic and clinical data had some limitations.

Second, this is a small population study, despite the fact that our study population is larger than that of previous studies of LMI. Thus, demonstrating statistical significance may be difficult. Larger multicenter studies with an adequate population size are necessary to elucidate the prognosis or etiological mechanisms for patients suffering from LMI.

CONCLUSION

This retrospective study revealed different stroke mechanisms and favorable outcomes in young patients with LMI. The young patients showed less frequent medical complications. Age is a significant prognostic factor for good functional outcome after LMI, regardless of other demographical or clinical characteristics. The arterial dissection was more frequent in young patients, so it is reasonable to evaluate VA or PICA by conventional angiography combined with MR angiography in young age patients with LMI.

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국문 초록

서론: 이전에 외측 연수 경색에서 젊은 환자와 노령 환자의 뇌졸중 발생 기전과 예후에 관련된 연구는 많지 않았다. 이에 본 연구에서는 외측 연수 경색 환자에서 연령에 따른 위험인자, 원인 및 예후의 차이점을 조사 하였다.

방법: 2004 년 2 월부터 2011 년 1 월까지 증상 발생 7 일 이내에 입원한 외측 연수 경색 환자들의 기록을 후향적으로 검토 및 조사를 하였다. 증상 발생 1 년간 신경학적인 결과를 바델 지수와 변형랜킨척도를 이용하여 평가 하였다. 또한 증상 발생 1 년간의 임상 사례를 확인하였다. 환자는 연령에 따라 두 그룹: 18-59 세(젊은 연령), 60 세 이상(노령)으로 나누었다. 또한 환자는 신경학적인 결과에 따라 좋은 예후(변형랜킨척도 0-1, 바델지수 95-100) 그룹과 나쁜 예후(변형랜킨척도 2-6, 바델지수<95) 그룹으로 나누었다. 환자들은 혈관 병변을 평가하지 위하여 뇌 자이 공명 혈관 조영검사와 혈관 조영술을 시행하였다.

결과: 본 연구에서는 총 106 명의 환자가 포함되었고 이 중 젊은 연령 그룹에는 37 명의 환자, 노령 그룹에는 69 명의 환자가 속하게 되었다. 본 연구에서 가장 흔한 뇌경색 기전은 양 그룹 모두에서 큰 동맥 죽상 경화증이(젊은 연령 그룹 45.9%, 노령 그룹 75.4%) 관찰되었다. 동맥 박리와 소혈관 폐색은 젊은 연령 그룹에서 많이

발생하였다. (동맥 박리 29.7% 대 2.9%, 소혈관 폐색 24.3% 대 8.7%) 폐렴은 나쁜 예후 그룹 (변형랜킨척도 ≥2) 에서 유의하게 많이 발생하였다. 다변량 로지스틱 회귀분석을 통하여 연령이 1 년의 나쁜 예후에 중요한 예측 인자인 것으로 확인하였다.

결론: 본 후향적인 연구는 젊은 연령의 외측 연수 경색 환자들이 좋은 예후와 결과를 보이는 것을 확인하였다. 젊은 연령 임상양상이나 여러 요인들의 효과에 독립적으로 외측 연수 경색 이후에 좋은 기능적인 예후의 예측인자일 수 있다. 동맥 박리와 소혈관 폐색은 젊은 연령 환자에서 중요한 뇌졸중 메커니즘이다. 따라서 젊은 외측 연수 경색 환자들은 뇌졸중 메커니즘을 확인하기 위해 자세한 진단 평가가 필요하다.

주요어 : 연령, 외측 연수 경색, 예후, 뇌졸중 메커니즘

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