Differences in Clinical Features and Computed Tomographic Findings between Embolic and Non-Embolic Acute Ischemic Stroke: A Quantitative Differential Diagnosis

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A diagnosis based on the presumed mechanism of stroke onset is useful for management strategies in acute ischemic stroke. Ninety-two patients with embolic (cardiac or artery-to-artery) and 107 with non-embolic (thrombotic or hemodynamic) stroke were diagnosed on strict cerebral angiographic criteria alone. To clearly discriminate between these two groups, the neurological and computed tomographic (CT) findings were then compared. Rapidity of onset, vomiting, urinary incontinence, level of consciousness, cervical bruit, anisocoria, tongue deviation, sensory disturbance, and CT findings (location of hypodense area, findings of brain edema and hemorrhagic transformation) were discriminatory factors between the two groups ($p < 0.01$). According to these 11 items, we prepared a numerical table for quantitative differential diagnosis. A diagnostic accuracy of 98.9% for embolic and 87.9% for non-embolic stroke in internal verification, and 90.0% and 82.9%, respectively, in external verification was observed. The differences in clinical features and CT findings between embolic and non-embolic stroke may reflect the pathophysiological mechanisms of the occlusive process of cerebral artery as well as the extent and severity of ischemia.

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Key words: cerebral angiography, cerebral embolism, cerebral thrombosis, discriminatory analysis, multivariate analysis, quantification theory

Introduction

Acute stroke remains a challenge for stroke neurologists. Neuroprotective and thrombolytic agents are currently being investigated regarding efficacy and safety in acute ischemic stroke. To achieve this goal, accurate clinical diagnosis should be necessary. Acute ischemic stroke can be classified not only into clinical categories, such as cardioembolic, atherothrombotic and lacunar stroke, but also by pathophysiological mechanism, i.e. embolic, thrombotic, or hemodynamic (1). Differentiation of embolic stroke from thrombotic or hemodynamic stroke is particularly important (2–5), because the strategies for management during the acute stage differ, based on the mechanisms of stroke onset rather than clinical subtypes. Subcategorization based on pathophysiological mechanisms can be more valuable in hyperacute ischemic stroke (e.g. regarding an application of thrombolytic therapy). However, differentiation of the pathophysiological mechanisms during the acute stage is often diffi-

cult. Clinical diagnostic criteria for embolic stroke have been proposed, mainly for cardioembolic stroke (1–7), whereas the characteristics, severity and treatment appear somewhat different between cardiogenic and artery-to-artery brain embolism (8). There are no useful clinical diagnostic criteria for non-embolic stroke, which has different mechanisms, thrombotic and hemodynamic, however, there have been a few reports suggesting differences in the clinical features according to pathogenetic and pathophysiological mechanisms among embolic and thrombotic or hemodynamic stroke (2–5).

Neuroimaging has been revolutionized over the last two decades, and recent advances of magnetic resonance imaging technology, particularly diffusion-weighted imaging, allow investigators to depict ischemic lesions *in vivo* during very early stages of acute ischemic stroke (9–14). Computed tomography (CT), however, can be still useful in hyperacute ischemic stroke for the following reasons; 1) to identify hemorrhagic and ischemic stroke accurately, particularly before thrombolytic

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treatment in hyperacute ischemic stroke, 2) it is simple, fast and available in all emergency hospitals, and 3) allows us to suggest embolic or non-embolic mechanisms when CT findings are typical as previously reported (15–19).

If simple, accurate and reliable clinical diagnostic criteria, such as a numerical table, for pathophysiological mechanisms of acute ischemic stroke were available, it would be of great use in clinical practice (20–24). To try and achieve this goal, it is necessary to clarify the differences in the clinical features and the neuroradiological findings between embolic and non-embolic stroke. A numerical table prepared by a statistical approach could lead to enhanced diagnostic accuracy, but unfortunately most numerical tables are not statistically derived. We attempted to determine the characteristic clinical features of embolic and thrombotic or hemodynamic stroke, and investigated the possibility of clinical differentiation by quantitative diagnosis.

Subjects and Methods

Patients selection

The subjects consisted of 435 consecutive ischemic stroke patients with the internal carotid arterial distribution, who were admitted to the Stroke Care Unit of the National Cardiovascular Center within seven days after onset between May 1978 and January 1989. During this period, initial (within seven days after the onset of stroke) and follow-up cerebral angiographies (CAG) were performed in 377 patients (86.7%). For the 377 patients, we attempted to determine the pathophysiological mechanisms of acute ischemic stroke, such as embolic, thrombotic or hemodynamic on the basis of CAG findings alone (25).

Subjects were selected based on the following CAG criteria alone. Patients showing an embolus shadow, which is a filling defect with trimming, in the initial CAG or reopening of a previously occluded cerebral artery in a follow-up CAG without significant arteriosclerotic changes (wall irregularity) were diagnosed as embolic stroke (EM) (26–28). Absence of arterial occlusion on the initial CAG, which implies an early reopening of the embolic occlusion was not used for criteria of EM. Because thrombotic and hemodynamic strokes based on atherosclerotic occlusive disease are occasionally difficult to differentiate by CAG alone, we assigned patients with a thrombotic or hemodynamic stroke to the non-embolic stroke (NE) category. Thus, patients with cardioembolic stroke and atherothrombotic stroke due to artery-to-artery embolism were categorized as EM, while the remaining atherothrombotic stroke patients due to thrombotic and hemodynamic mechanisms were NE. Criteria for the angiographic diagnosis of NE by CAG included an occlusion of a major cerebral artery associated with atherosclerotic changes (wall irregularity), i.e. stump or tapering occlusion at the origin of internal carotid artery (ICA) or the proximal stem (origin) of the middle cerebral artery (MCA) (3, 29). Occlusion of the MCA branch with marked arterial wall irregularity was also considered as atherosclerotic in nature (29). No embolus shadow in the initial CAG or reopening phenomenon on a follow-up CAG was included for NE. Table 1 summarizes

Table 1. Angiographic Findings in Embolic Stroke and Non-Embolic Stroke

	Embolic stroke (n=92)	Non-embolic stroke (n=107)
Site of occlusion		
ICA occlusion	26 (28.3)	44 (41.1)
proximal (extracranial)	4	44
distal (intracranial)	22	0
MCA stem occlusion	23 (25.0)	46 (43.0)
MCA branch occlusion	30 (32.6)	10 (9.3)
Multivessel occlusion	13 (14.1)	7 (6.5)
Specific findings		
Embolus shadow with reopening	20 (21.7)	0 (0)
Embolus shadow without reopening	21 (22.8)	0 (0)
Reopening without embolus shadow	51 (55.4)	0 (0)

Numbers in parentheses are percentages, ICA: internal carotid artery, MCA: middle cerebral artery.

the angiographic findings of the two groups. One hundred and ninety-nine patients were included in this study, 92 cases with EM (average 62.1 ± 11.7 years, 43 men and 49 women) and 107 with NE (average 63.8 ± 9.9 years, 81 men and 26 women). In EM, 71 of 92 (77.2%) cases showed complete reopening of previously occluded cerebral arteries, while the remaining 21 cases (22.8%) without re-opening were diagnosed as EM based on embolus shadow. For NE, 84.1% of patients showed a major cerebral arterial occlusion, while in EM 32.6% and 14.1% were found to have MCA branch occlusion and multi-vessel occlusion, respectively. Brain CT and the clinical features were not considered at all in the patients selection.

Variables used for comparison

The incidence for each category of the temporal profile, physical findings and neurological findings were retrospectively analyzed (Tables 2, 3), as derived from the patients' clinical records. The results of routine laboratory examinations on admission were also studied (Table 4). To compare the CT findings between EM and NE, the location and configuration of hypodense areas and the presence of brain edema or hemorrhagic transformation were examined on the initial CT (Table 5) as described in previous reports (15–18, 30–32). Initial CTs were performed on the average 4.0 days after onset of EM, and 4.1 days in NE. Infarct index was also calculated as a ratio of the hypodense area to the homolateral hemispheric area, and expressed in percent (3). These analyses were performed without CAG information.

Quantitative differentiation table

Values are expressed as mean $\pm$ SD. Statistical analyses were performed by a chi-square test, two-tailed unpaired *t*-test, and Hayashi's quantification theory group II (33, 34). A *p*-value

Embolic Score in Acute Ischemic Stroke

Table 2. Physiological Findings and Temporal Profile

	Embolic stroke (n=92)	Non-embolic stroke (n=107)	p-value
Body weight (kg)	52.7 ± 1.0	54.8 ± 1.0	NS
Respiration rate (min ⁻¹)	18.4 ± 0.4	17.0 ± 0.3	p<0.01
Blood pressure (mmHg)			
Systolic	146.6 ± 25.6	162.7 ± 25.1	p<0.01
Diastolic	85.1 ± 14.8	89.6 ± 14.7	p<0.01
Previous TIA			
Total	9 (9.8)	24 (22.4)	p<0.01
Stereotype	4	22	
Multivessels	5	2	
Rapidity of onset			p<0.01
Abrupt	66 (71.7)	10 (9.3)	
Insidious	3 (3.3)	34 (31.8)	
Stepwise	4 (4.3)	48 (44.9)	
Unknown	19 (20.7)	15 (14.0)	
Time of onset			p<0.01
Active	64 (69.6)	56 (52.3)	
At morning	6 (6.5)	41 (38.3)	
During sleep	15 (16.3)	8 (7.5)	
Unknown	7 (7.6)	2 (1.9)	

Numbers in parentheses are percentages. Statistical analyses are chi-square test and two-tailed unpaired *t*-test. TIA: transient ischemic attack, NS: not significant.

Table 3. Neurological Findings in Embolic Stroke and Non-Embolic Stroke

	Embolic stroke (n=92)		Non-embolic stroke (n=107)		
	yes	unknown	yes	unknown	
Level of consciousness ^a					
Alert	10 (10.9)		33 (30.8)		
Confusion	39 (42.4)		57 (53.3)		
Somnolent	34 (37.0)		16 (15.0)		
Coma	9 (9.8)		1 (0.9)		
Headache	16/72 (22.2)	20	16/93 (17.2)	14	
Vomiting ^a	16/80 (20.0)	12	4/99 (4.0)	8	
Convulsion ^c	4/76 (5.3)	16	0/98 (0.0)	9	
Incontinence ^a	25/72 (34.7)	20	15/100 (15.0)	7	
Cervical bruit ^a	4/92 (4.3)	0	18/107 (16.8)	0	
Aphasia	31/71 (43.7)	21	41/94 (43.6)	13	
Conjugate deviation ^a	50/92 (54.3)	0	25/107 (23.4)	0	
Anisocoria ^a	23/92 (25.0)	0	4/107 (3.7)	0	
Horner's syndrome	15		2		
III palsy	8		2		
Absent light reflex ^b	8/92 (8.7)	0	1/107 (0.9)	0	
VII palsy ^a	77/85 (90.6)	7	81/104 (77.9)	3	
XII palsy ^a	38/53 (71.7)	39	34/90 (37.8)	17	
Motor paresis	88/92 (95.7)	0	102/107 (95.3)	0	
Sensory disturbance ^a	57/65 (87.7)	27	44/91 (48.4)	16	
Pathological reflex ^c	71/92 (77.2)	0	67/106 (63.2)	1	

Numbers in parentheses are percentages. ^a, p<0.01, ^b, p<0.02, ^c, p<0.05, respectively, by chi-square test.

Table 4. Laboratory Examinations in Embolic Stroke and Non-Embolic Stroke

	Embolic stroke (n=92)	Non-embolic stroke (n=107)	Normal range
Leukocyte (10 ³ /μl)	9.4 ± 3.1	8.9 ± 2.6	4.0–9.0
Erythrocyte (10 ⁴ /μl)	451.0 ± 54.1	467.5 ± 67.3	420–550
Hematocrit (%) ^c	41.7 ± 5.0	43.3 ± 5.9	36.0–54.0
Thrombocyte (10 ⁴ /μl)	18.8 ± 7.5	21.0 ± 6.6	15.0–35.0
Serum sodium (mEq/l)	138.1 ± 3.5	138.5 ± 4.3	138–145
Serum potassium (mEq/l)	3.9 ± 0.5	3.8 ± 0.4	3.4–4.9
Total protein (g/dl)	7.4 ± 0.8	7.2 ± 0.7	6.5–8.2
Fasting blood sugar (mg/dl)	138.6 ± 39.5	129.5 ± 47.3	65–110
GOT (U/l)	35.1 ± 17.6	30.4 ± 21.6	0–40
CPK (U/l)	182.5 ± 269.3	133.3 ± 150.4	40–160
Total cholesterol (mg/dl)	186.4 ± 36.5	195.4 ± 50.0	130–250
Triglyceride (mg/dl) ^b	105.1 ± 56.0	131.2 ± 71.3	80–160
Prothrombin time (%) ^a	80.9 ± 26.0	95.3 ± 17.3	76–132
Fibrinogen (mg/dl)	348.7 ± 123.8	331.6 ± 99.2	152–260
ESR (mm)			
1 hour	19.8 ± 19.4	18.9 ± 17.2	–
2 hours	44.4 ± 31.7	43.2 ± 28.0	–

Values are mean ± SD. ^a, p<0.001, ^b, p<0.01, ^c, p<0.05, respectively, by *t*-test. GOT: glutamic oxaloacetic transaminase, CPK: creatine phosphokinase, ESR: erythrocyte sedimentation ratio.

Table 5. CT Findings in Embolic Stroke and Non-Embolic Stroke

	Embolic stroke (n=92)	Non-embolic stroke (n=107)
Location (site of lesion) ^a		
No lesion	3 (3.3)	4 (3.7)
Cortical*	73 (79.3)	32 (29.9)
Subcortical	14 (15.2)	24 (22.4)
Watershed area	0 (0.0)	39 (36.4)
Superficial		12
Deep		3
Superficial and deep		24
Unclassified cortical	2 (2.2)	8 (7.5)
Brain edema ^a		
No edema	10 (10.9)	39 (36.4)
Moderate [†]	36 (39.1)	53 (49.5)
Midline-shift	43 (46.7)	11 (10.3)
Margin of hypodense area ^a		
Clear	60 (65.2)	29 (27.1)
Unclear	29 (31.5)	74 (69.2)
Hemorrhagic transformation ^a		
Within seven days of onset	9 (9.8)	1 (1.0)
Total (during observation)	38 (41.3)	5 (4.7)
Infarct Index (%) ^b	30.6 ± 23.9	13.2 ± 13.5

*Confined with vascular territories. [†]Deformity of the lateral ventricle or disappearance of the cortical sulci on the affected hemisphere is classified as moderate brain edema. Numbers in parentheses are percentages. Values are mean ± SD. ^a, p<0.01 by chi-square test, and ^b, p<0.0001 by *t*-test.

of less than 0.05 was considered as statistically significant.

Preparation of a differentiation table to identify embolic from non-embolic stroke was attempted on the basis of the results obtained in the present study. In preparation of the quantitative table, 52 patients with EM and 66 patients with NE up to 1982 while the CT device was an EMI 1010 (Toshiba Co. Ltd., Tokyo) were applied. These patients were also used for an internal verification. External check was performed in 40 patients with EM and 41 patients with NE from 1983 when a TCT 20A (Toshiba Co. Ltd., Tokyo) was used.

The incidence of each category of items for the temporal profile, physical, neurological and CT findings were calculated and statistically compared between EM and NE using a chi-square test, as described in the previous section (Tables 2, 3, and 5). A preliminary discriminatory analysis was performed on items for which statistical significance was obtained, and a combination of those items that contribute to an improvement of the probability for correct diagnosis was determined. When some items were lacking due to insufficient information in the acute stage, they were categorized as "unknown". The system was simplified as much as possible to make evaluations of each item easier even for the general practitioner. The items and categories obtained were analyzed by Hayashi's quantification theory group II (33, 34).

Hayashi's quantification theory group II

When external bases (objective variables) are given as qualitative data in regression analysis, the discriminatory analysis is to be used as the statistical method which explains the external bases on the basis of quantitative items (explanatory variables). On the other hand, the statistical method appropriate to explain the external bases given qualitatively on the basis of qualitative items is the quantification theory group II (33). Application of this discriminatory function method using the categorical data as the variables is statistically optimum for preparation of a differentiation table.

The items (clinical features and CT findings) which were considered to influence the external base consisting of a group of k ($k=2$; EM and NE in the present study) are set. Then, suppose that the number of items is given as m ($m=11$, see Results) and the number of categories for each item as $n_1, n_2, \dots, n_m$. The values of case s in group k (EM or NE) relative to the j -th category of the i -th item may be expressed in the following dummy variable:

$$\delta_{ij}^{ks} = \begin{cases} 1: & \text{when case } s \text{ in group } k \text{ responds to } j\text{-th category} \\ & \text{of } i\text{-th item,} \\ 0: & \text{otherwise.} \end{cases}$$

Each item is assumed to respond to one category, but not to the other category. It may be assumed that these item-category data of each case can be obtained by a linear formula of the first degree:

$$Y_{ks} = \sum_{i=1}^m \sum_{j=1}^{n_i} \alpha_{ij} \delta_{ij}^{ks}$$

The coefficient α_{ij} (category weight) can be considered as the qualitative weight given to the item-category. Then, the category weight, α_{ij} is determined so that the weight, Y_{ks} is small when the cases belong to the same group and large when they belong to different groups. This is equivalent to obtaining the category weight with the maximum correlation ratio (η^2). The total variance (σ_T^2) of Y_{ks} is obtained from the sum of the between-group variance (σ_B^2) and the within-group variance (σ_W^2). Therefore,

$$1 = \sigma_B^2 / \sigma_T^2 + \sigma_W^2 / \sigma_T^2$$

The correlation ratio (η^2) is expressed as σ_B^2 / σ_T^2 , and the values are in the range 0 to 1. Since σ_W^2 approaches 0 as η^2 approaches 1, this means that the k groups are separated.

The degree of influence of an item on the external bases is shown by the range of the category weights in the respective item. The degree of influence of each category in a given item on the external base is evident from the value of the category weight. In the same way as in regression analysis, it is possible to obtain the partial correlation coefficients between each item and external bases. The accuracy of the results of analysis is shown by the correlation ratio (η^2) or the multiple correlation coefficient (η).

Results

Patients' baseline profiles

Table 2 shows the clinical and laboratory findings for 92 patients with EM and 107 patients with NE. For EM, 79 patients (85.9%) with potential cardiac sources of emboli were diagnosed as cardioembolic stroke. The respiration rate on admission was significantly higher in EM ($p<0.01$), while arterial blood pressure, both systolic and diastolic, was significantly higher in NE, 162.7 ± 25.1 mmHg and 89.6 ± 14.7 , than in EM, 146.6 ± 25.6 and 85.1 ± 14.8 ($p<0.01$). Previous transient ischemic attack (TIA) was found in 22.4% of NE, but in only 9.8% in EM. All TIAs in NE were stereotype, while more than one-half of TIAs in EM occurred in multiple vessels (Table 2). Abrupt onset of neurologic deficits was seen in 71.7% of EM, and many "unknown" cases with EM were found with a severe defect that suggested sudden onset with maximal neurologic deficits. An abrupt onset was reported in only 9.3% in NE. The time of onset in more than one-half of the patients in both groups was during daytime while active.

Neurological findings

The neurological findings in EM and NE are shown in Table 3. The level of consciousness on admission was more severely disturbed in EM in contrast to those in NE; i.e. somnolent in 37.0% and comatose in 9.8% in the former, and alert in 30.8% and confused in 53.3% in the latter ($p<0.01$). Patients with EM showed a significantly high incidence of vomiting and incontinence at onset ($p<0.01$, $p<0.01$, respectively). A cervical bruit was noted in 18 patients (16.8%) in NE but in only four (4.3%) in EM ($p<0.01$). No significant difference in the frequency of aphasia was observed between the two groups.

Conjugate eye deviation was significantly more common in

EM (54.3%) in comparison to NE (23.4%) ($p<0.01$). It was evident that hemispheric symptoms and signs were more extensive and severe in EM. Horner's syndrome was found in 15 patients (16.3%) in EM but in only two (1.9%) in NE. Thus, anisocoria in the acute stage was more frequently seen in EM than NE (25.0% vs. 3.7%) ($p<0.01$). Among abnormalities of the pupils, mydriasis associated with an absent pupillary light reflex due to oculomotor palsy was observed in eight patients (8.7%) with EM, but in only two (1.9%) with NE. Central VII nerve palsy, XII nerve palsy, sensory disturbance and Babinski's sign were significantly more common in EM than in NE ($p<0.01$, 0.01, 0.01, 0.05, respectively).

Laboratory examinations

The results of routine laboratory examinations on admission are shown in Table 4. Hematocrit was significantly higher in NE ($p<0.05$), while the prothrombin time was significantly prolonged in EM ($p<0.001$). However, the mean values of these variables were rather similar between the two groups and within the normal range, suggesting that these conventional parameters are not useful for identifying the pathophysiological mechanisms of stroke onset.

Brain CT findings

A summary of CT findings is shown in Table 5. A cortical hypodense area in a single vascular territory, a well marginated lesion, shift of midline structures (suggesting brain edema) and hemorrhagic transformation were significantly more prevalent in EM ($p<0.01$, respectively). The infarct index was significantly greater in EM than in NE with mean values of 30.6% and 13.2%, respectively ($p<0.0001$). When CT taken eight days after the onset was considered, hemorrhagic infarction was present in 38 patients with EM (41.3%). Infarcts in the basal ganglia and/or deep white matter were present in 24 patients with NE (22.4%) and 14 patients with EM (15.2%). Watershed infarction on CT was found in 39 patients with NE (36.4%); 22 with ICA occlusion and 17 with MCA stem occlusion. Of 39 watershed infarctions, 27 patients (69.2%) showed the deep watershed infarction ($n=3$) or the superficial and deep watershed infarction ($n=24$). No watershed infarction was observed in EM.

Quantitative differentiation table

The category weights were calculated for each category of the respective 11 items which finally were selected by the quantification theory group II. The sample scores were 0.98 ± 0.45 for EM and -0.77 ± 0.53 for NE. The difference in the mean values was 1.75 and the discriminatory point obtained from the cumulative distribution was 0.031. There was a good discrimination between EM and NE as the external bases with a correlation ratio of $\eta^2=0.76$ and multiple correlation coefficient $R=0.87$.

The quantitative table was prepared by multiplying each category weight by 10 and rounding off the figures. Table 6 shows the numerical table (Embolus Score). When the total of scores in the 11 items was zero or greater, the patient was

evaluated as EM, and when it was a negative number the evaluation was NE. The result of internal check revealed that the diagnostic accuracy was 98.9% for EM and 87.9% for NE. For the external verification, 40 patients with EM and 41 with NE during the year of 1983 and 1989 were studied. No significant differences were observed in any of the items in these two study periods (data not shown). With the external check, a favorable diagnostic accuracy of 90.0% for EM and 82.9% for NE were obtained.

Of 92 cases with EM, misdiagnosis by "Embolus Score" was found in five patients with mild neurologic deficits, who had a MCA branch occlusion. Diagnosis was incorrect in 15 of 107 cases with NE. Twelve of these had aphasia and disturbance of consciousness, suggesting the presence of extensive ischemia.

Discussion

In the present study, differences in temporal profile, physical, neurological and CT findings between EM and NE appear to depend on the pathophysiological mechanisms of each stroke subtype, i.e. the time course until cerebral arterial occlusion, the site of arterial occlusion and the state of the collateral circulation. Angiographic features of embolic stroke are as follows: 1) an abrupt arterial occlusion, 2) occlusion at the site just prior to arterial branching in the distal end of the ICA or MCA stem, or occlusion in the MCA branch, 3) absent or insufficient collateral circulation via the circle of Willis or leptomeningeal anastomoses, 4) frequent reopening phenomenon of the occluded vessel, and 5) frequent multiple arterial occlusions due to breakdown of the embolus (2–8, 26). The main radiographic features of thrombotic or hemodynamic stroke are as follows: 1) a gradual obstruction with thrombus formation on the atheromatous plaque, 2) an occlusion at the origin of ICA or MCA stem, 3) influence of hemodynamic factors such as grade of stenosis and/or collateral circulations via the circle of Willis or leptomeningeal anastomoses (3, 4, 29).

A comprehensive clinical diagnosis of stroke subtypes is made in accordance with the temporal profile, neurological findings and the presence of cardiac disorders, systemic embolism or other risk factors, because there is no clinical "gold standard" for each stroke subtype other than pathological verification. Classification of stroke subtypes using CAG alone has some disadvantages, because an embolic stroke patient without reopening or an embolus shadow can potentially be diagnosed as NE. In clinical practice, however, conventional CAG can demonstrate the mechanisms of cerebral arterial occlusion more accurately than any other clinical tools (25), although Duplex carotid ultrasonography, transcranial Doppler ultrasonics, and magnetic resonance angiography are taking the place of this invasive examination. Thus, we used CAG for classification of the pathophysiological mechanisms to clarify and determine the differences in clinical features and CT findings.

Clinical features and neurological findings

With respect to the mode of onset, a progressive (insidious

and stepwise) course was observed in 76.5% of NE, whereas 71.7% of patients with EM showed an abrupt onset. According to the statistical analysis used in the present study, the most useful item in discrimination between EM and NE was the rapidity of onset, as shown in Table 6. This indicates that the differences in the temporal profiles in the acute phase between EM and NE do not reflect the patients' background factors such as risk factors but rather they reflect the process of arterial occlusion. On the other hand, the differences in the respiration rate, vomiting, incontinence, consciousness disturbance, motor weakness and sensory disturbances between EM and NE can be

explained mainly by the extent of infarct and the severity of brain ischemia.

Ocular symptoms and signs are also quite important for differential diagnosis in the acute stage of ischemic stroke. Conjugate deviation was found significantly more frequent in EM than NE, compatible with the more extensive and severe ischemia in EM. Anisocoria in the acute stage is observed in the presence of uncal (tentorial) herniation or Horner's syndrome on the affected side, and was significantly more common in EM. Horner's syndrome in cerebrovascular disease is known to be caused by brain stem infarction, but there have been a few detailed studies concerning supratentorial brain infarction in the internal carotid arterial system (35). The postganglionic fibers of the superior cervical sympathetic ganglia are divided into those which run upwards along the external carotid artery, controlling facial perspiration and vasomotor function, and those which run upwards around ICA, controlling the pupils, eyelids and perspiration of the forehead (35). The reason for a high incidence (16.3%) of partial Horner's syndrome in EM may be sudden damage (or ischemia) to the local postganglionic fibers when the embolus passes through or obstructs ICA. It is also suggested that the presence of supratentorial infarct lesions which expand towards the ipsilateral thalamus is one of the causative mechanisms for Horner's syndrome.

Table 6. "Embolitic Score" for Identifying Embolic Stroke from Non-Embolitic Stroke

1. Manner of onset	Abrupt	5
	Insidious/Stuttering	-6
	Unknown	4
2. Vomiting at onset	Yes	5
	No	-1
	Unknown	0
3. Incontinence at onset	Yes	2
	No	-2
	Unknown	1
4. Level of consciousness on admission	Alert	-1
	Confusion	0
	Drowsy/Coma	2
5. Cervical bruit	Yes	-2
	No	0
6. Anisocoria	Yes	3
	No	-1
7. Deviation of the tongue	Yes	2
	No	-3
8. Sensory disturbance	Yes	1
	No	-1
	Unknown	3
9. Location of the infarction on CT	Cortical	2
	Deep seated	1
	Watershed	-2
	Miscellaneous	-1
	None	-4
10. Brain edema on CT	No edema	-1
	Moderate	0
	Midline-shift	1
11. Hemorrhagic transformation on CT	Yes	4
	No	0

Sum of all items ≥ 0 ; regarded as Embolic Stroke. < 0 ; regarded as Thrombotic or Hemodynamic Stroke.

Laboratory examinations

The hematocrit was greater in NE than EM, suggesting that rheological factor may have been partly related to the development of non-embolic stroke (36, 37). However, these conventional laboratory studies were not useful for identifying embolic from non-embolic stroke, because differences in the mean value of each variable were close and within the normal range. Our earlier study demonstrated that measurement of hemostatic molecular markers, such as thrombin-antithrombin III complex and D-dimer are useful to differentiate with high accuracy cardioembolic stroke from the other stroke subtypes in the hyper acute stage (38), although such novel molecular markers are not generally available in clinical practice at present.

Brain CT findings

Cortical infarction confined to a vascular territory, shift of midline structure and hemorrhagic transformation on CT were observed in EM with a significantly high incidence, and these results are consistent with the previous observations (15-18, 30-32). A well-marginated cortical infarction confined to a vascular territory appears to reflect a distinct difference between infarcted and preserved brain tissue, since the ischemic injury in the embolic mechanism matches the territory of a cerebral artery (16, 18). However, the frequency of hemorrhagic transformation detected by CT is not very high within seven days of onset and requires very frequent and careful examination. Diagnostic accuracy is improved when hemorrhagic infarctions are detected after seven days and added to "Embolitic Score".

Watershed infarction is known to be caused by atherothrombotic ICA occlusion with hemodynamic compro-

mise, although the pathophysiology remains unclarified (30, 39–43). Among 39 cases with watershed infarction in the present series, MCA stem occlusion was found in 17 cases as well as 22 cases of ICA occlusion in NE. The evidence suggests that watershed infarction is caused not only by hemodynamic mechanism but also by multiple factors such as embolism, multiple microemboli or blood coagulation disorders (41, 43). Infarcts involving the deep watershed area were present in 27 of 39 NE cases (69.2%). We found that an infarction in the deep watershed area was characteristic of atherothrombotic brain infarction, while a superficial watershed infarction was also seen in 1.5% of embolic stroke in our another series (18).

Quantitative differentiation table

Numerical tables are widely used in clinical practice or research to diagnose stroke subtypes or to grade the severity of the illness (20–24), although some quantitative diagnostic criteria are not based on statistics. To prepare a numerical table for differential diagnosis, we used the quantification theory group II, because the external bases given qualitatively should be explained on the basis of qualitative factors, as mentioned in Methods (33, 34). “Embolus Score” derived in this study, showed a high diagnostic accuracy beyond 80% with internal and external verifications, and appeared to be useful for actual quantitative diagnosis. In EM, only five cases (5.4%) were totally misdiagnosed. On the other hand, 15 cases (14.0%) with NE who showed hemispheric syndromes, such as aphasia or consciousness disturbance were misdiagnosed as EM. Possible reasons are as follows: 1) diversification of the ischemic lesion depending on the mode of atherosclerotic arterial occlusion and the development of collateral circulations, 2) inclusion of thrombotic stroke patients with sudden arterial occlusion, such as rupture of atheromatous plaque, and 3) the presence of artery-to-artery embolism peripheral to the site of occlusion. Thus, the pathophysiology and pathogenetic mechanisms of thrombotic and hemodynamic strokes are much more heterogeneous. It is well known that atherothrombotic ICA occlusion may occur in the setting of acute stroke or may occur gradually or silently, depending on the intracranial collateral circulation (29).

Conclusion

From the present study, it was evident that the differences in clinical features and CT findings between EM and NE do not reflect the patients' backgrounds, rather they reflect the pathophysiological mechanisms of cerebral arterial occlusion at onset of stroke, that regulate the extent and severity of the ischemic lesion. Thus, investigations of therapeutic strategies during the acute stage based on the pathophysiological mechanisms may be more important than clinical categories, because clinical subtypes include various mechanisms of stroke onset. The “Embolus Score” derived from this study with a high diagnostic accuracy might also be helpful in investigations of acute ischemic stroke.

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