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Re-evaluation of Clinical Features and Risk Factors of Acute Ischemic Stroke in Japanese Longevity Society

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ABSTRACT

Age is an important factor correlated with stroke prevalence and independently influences stroke outcome especially in Japanese longevity society. To re-evaluate the characteristics of acute ischemic stroke in the old-old, analyses of clinical data on 426 patients registered at a Japanese tertiary emergency hospital were performed under appropriate statistical methods. Clinical features, stroke subtypes, current-known risk factors for stroke, time from onset to arrival, the National Institute of Health Stroke scale (NIHSS) score on admission, length of hospital stay, modified Rankin Scale (mRS) at discharge were compared between two stratified groups by age-at-onset (≧75 and < 75 years old). Significant differences were demonstrated in categories of sex, NIHSS score, length of hospital stay and m-RS. Current-known risk factors for stroke except atrial fibrillation were not prominent in the elderly group. Our study revealed that clinical phenotype and outcome in stroke patients would have been modified and re-evaluation of risk factors is necessary for prevention of ischemic stroke in Japanese longevity society.

INTRODUCTION

Stroke is one of the leading causes of mortality and patients with stroke suffer from long-term physical and mental disabilities. Medical cost for treatment and care for patients with stroke is increasing in Japanese longevity society. Age *per se* is an important independent risk factor for stroke. Some studies showed old age groups have different risk profile and stroke features compared to the young group in longevity society (17, 19, 6, 27, 23). There are few studies on acute ischemic stroke in old people in Asian countries (17), compared with European and other countries (19, 6, 27, 23). In April 2008, the Japanese government introduced a new medical program for the elderly to save medical cost. Old-old adults medical care program (the late-stage medical care system for the elderly) covers persons aged 75 and more. Purpose of our investigation is to re-evaluate the current-known risk factors, clinical features, and outcome for acute ischemic stroke in patients older than 75 years of age as compared with patients under 75 years of age in Japanese longevity society.

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PATIENTS AND METHODS

Background of Patients

This study retrospectively reviewed the record of acute ischemic stroke patients admitted to the Hyogo Brain and Heart Center at Himeji from January 2007 to December 2008. Himeji, situated in the western area (Kansai district) of the main island of Japan, is a typical Japanese city with an area of 534 km^2 including industrial, commercial, agricultural and residential areas, and population of approximately 536,000. The Hyogo Brain and Heart Center at Himeji is the only tertiary emergency hospital serving acute stroke treatments over Himeji city. It has eight major departments (cardiology, cardiovascular surgery, neurology, neurosurgery, general internal medicine, general surgery, anesthesiology and radiology). Our neurology service team consists of six physicians (five board-certified neurologists and one resident) with four neurological intensive care beds and 48 ward beds, providing 24-h intensive care including intravenous tissue plasminogen activator (t-PA) therapy. Neuroradiological facilities available 24-hours include computed tomography (CT), angiographic system and magnetic resonance imaging (MRI) with the capability of MR angiography.

Clinical Analysis of Patients

All patients were subject to electrocardiogram (ECG), chest radiography and routine laboratory examination on admission. Patients were also subject to examination of brain MRI to confirm stroke subtype. Hypertension, diabetes mellitus, hyperlipidemia were diagnosed as described elsewhere (13,16,4). Atrial fiblliration was diagnosed in initial study of electrocardiography on admission. Smoking was defined when the patients consumed >5 cigarettes daily. Cognitive function was evaluated as described before (2,21). Severity of neurological deficits was assessed using the National Institute of Health Stroke Scale (NIHSS) (18). Outcome was assessed using modified Rankin Scale (m-RS) at discharge as follows: no symptom (mRS 0), symptom but no disability (mRS 1), mild disability (mRS 2) , moderate disability with independent walking (mRS 3), severe disability (mRS 4), bedridden state (mRS 5), and death (mRS 6) (30). Ischemic strokes were classified into the following four subtypes according to the TOAST (Trial of ORG 10172 in Acute Stroke Treatment) categories (1); lacunar, atherothrombotic, cardioembolic and others (other etiologies, unclassified or undetermined). In this study, at first, patients were divided into 2 groups based on the age on admission ($\geqq$75 and < 75 years old). Clinical features, stroke subtypes, risk factors, time from onset to arrival, NIHSS score on admission, length of hospital stay, mRS at discharge and medications for prevention of stroke were compared between two groups. Furthermore, effectiveness of warfarinization was evaluated by the prothrombin time international normalized ratio (PT-INR) values at admission. Secondary, the aged patients were further divided into 2 sub-groups on outcome (mRS:0-2 and 3-6). Patients with m-RS:0-2 were assigned to good outcome group and patients with m-RS:3-6 were assigned to poor outcome group. The factors described above were again compared between two sub-groups.

Statistical analyses

The two age groups were compared for each factor using univariate analysis. Significance was judged on the basis of the chi-square test for categorical variables and the Mann-Whitney test for continuous variables. Management and analyses of data were carried out using StatView version 5.0 (Statistical Analysis System (SAS). Cary, NC, USA). Significance level was determined as $p < 0.05$.

RESULTS

During the 24-month study period, 426 patients with ischemic stroke were admitted to our hospital, consisting of 199 (46.7%) aged ≧75 years, and 227 (53.3%) aged <75 years. Demographic variables and clinical features in the two age groups were described in the Table I. Ages-at-onset were 81.5 ± 4.8 and 64.4 ± 7.6 (mean ± standard deviation), respectively. Compared with the younger group, the patients in the older group were more often women (42.7% versus 26.9%, p= 0.0006). No significant difference was demonstrated in the categories of time from onset to arrival and stroke subtypes between the two age groups. Both NIHSS score on admission and m-RS at discharge were higher in the older group than younger group (p < 0.0001). Days of hospital stay were longer in the older group (p < 0.0001). Patients in the older group could less frequently go back their own home (p=0.0005).

Table I. Demographic variables and clinical features in the two age groups

	≧75 years old (n=199)	<75 years old (n=227)	p
Age	81.5±4.8	64.4±7.6	<0.0001
Female	85(42.7%)	61(26.9%)	0.0006
Time from onset to arrival			0.19
≦6h	105	105	
6-24h	58	68	
24h-7days	36	57	
Subtypes			0.17
Atherothrombotic	50	47	
Cardioembolic	78	77	
Lacunar	28	48	
Others	43	55	
NIHSS on Admission	9.0±10.0	4.6±6.2	<0.0001
Days of Hospital stay	28.4±24.2	21.5±17.0	<0.0001
m-RS at discharge	2.9±1.8	1.8±1.6	<0.0001
Outcome			0.0005
Back to their home	86	141	
Other hospital	105	81	
Death	8	5	

Results of comparison of risk factors for stroke in the two age groups were summarized in the Table II. Patients in the older group more frequently had atrial fibrillation (35.2% versus 24.7%, p= 0.018) and history of previous stroke (24.6 % versus 10.1%, p < 0.0001). On the other hand, the older group less often had hypertension (46.7% versus 60.8%, p= 0.0037), diabetes mellitus (19.6% versus 36.1%, p= 0.0002), hyperlipidemia (23.6% versus 34.4%, p=0.015) and smoking habit (19.6% versus 35.7%, p<0.0001). Analysis of medications for prevention of stroke at admission did not show any difference between the two groups , including warfarin, antiplatelet agent, angiotensin II receptor blocker and statin. Results of comparison of laboratory data in the two age groups were shown in the Table III. Serum total cholesterol (p=0.0089), serum triglycerides (p < 0.0001), blood sugar (p=0.018) and HbA1c (p < 0.0001) were significantly higher in the younger group. Serum high density lipoprotein (HDL) cholesterol tended to be higher in the younger group.

Table II. Risk factors of ischemic stroke in the two age groups

	≧75 years old (n=199)	<75 years old (n=227)	p
Hypertension	93(46.7%)	138(60.8%)	0.0037
Diabetes mellitus	39(19.6%)	82(36.1%)	0.0002
Hyperlipidemia	47(23.6%)	78(34.4%)	0.015
Atrial fibrillation	70(35.2%)	56(24.7%)	0.018
Smoking	39(19.6%)	81(35.7%)	<0.0001
Previous stroke	49(24.6%)	23(10.1%)	<0.0001
Medications on admission			
Warfarin	16(32.7%)	9(39.1%)	0.59
antiplatelet agents(※)	30(61.2%)	14(60.9%)	0.98
ARB	6(12.2%)	4(17.4%)	0.56
Statin	8(16.3%)	6(26.1%)	0.22

※ aspirin, ticlopidine, clopidgrel, cilostazol
ARB: angiotensin Ⅱreceptor blocker

Table III. Laboratory data of ischemic stroke in the two age groups

	≧75 years old (n=199)	<75 years old (n=227)	p
T-Cho.(mg/dl)	183.4±35.3	194.3±41.3	0.0089
HDL-C. (mg/dl)	45.5±12.2	48.5±16.5	0.064
LDL-C. (mg/dl)	117.0±29.7	120.5±38.1	0.38
TG (mg/dl)	99.7±50.0	124.8±62.8	<0.0001
BS (mg/dl)	137.5±46.0	147.0±56.0	0.018
HbA1c(%)	5.8±1.0	6.1±1.3	<0.0001

T-Cho: total choresterol, HDL-C: high density lipoprotein cholesterol,
LDL-C: low density lipoprotein cholesterol, TG: triglycerides, BS: blood sugar

Characteristics of the patients with atrial fibrillation in the two age groups were shown in the Table IV. Previous warfarin therapy in patients with atrial fibrillation tended to be fewer in the older group (30.0% versus 46.4%, p= 0.058). Average value of PT-INR at admission in the patients under warfarinization was significantly lower in the older group (1.34 ± 0.19 versus 1.57 ± 0.31, p= 0.0045). The patients who had PT-INR $\geqq 1.6$ as therapeutic range were few in the two age groups.

Table IV. Characteristics of the patients with atrial fibrillation in the two age groups

	≧75 years old (n=70)	<75 years old (n=56)	p
Previous warfarin	21(30.0%)	26(46.4%)	0.058
PT-INR≧1.6	3(14.3%)	9(34.6%)	0.18
PT-INR on admission	1.34±0.19	1.57±0.3	0.0045

PT-INR: prothrombin time international normalized ratio

Table V. Characteristics of older ischemic stroke patients in the two outcome groups

	Good outcome (m-RS:0-2) (n=86)	Poor outcome (m-RS:3-6) (n=113)	p
Age	80.9±4.5	82.0±4.9	0.083
Female	26(30.2%)	59(52.2%)	0.0019
Subtypes			0.0073
Atherothrombotic	18	32	
Cardioembolic	28	50	
Lacunar	20	8	
Others	20	23	
Living alone	14(16.3%)	14(12.4%)	0.43
NIHSS on Admission	3.3±4.8	13.3±10.8	<0.0001
Days of hospital stay	17.5±11.3	36.7±28.0	<0.0001
Hypertension	36(41.9%)	57(50.4%)	0.23
Diabetes mellitus	19(22.1%)	20(17.7%)	0.44
Hyperlipidemia	18(20.9%)	29(25.7%)	0.43
Atrial fibrillation	26(30.2%)	44(38.9%)	0.2
Smoking	19(22.1%)	20(17.7%)	0.44
Previous stroke	15(17.4%)	34(30.1%)	0.04
Cognitive impairment	4(4.7%)	10(8.8%)	0.25

Characteristics of older ischemic stroke patients in the two outcome groups were described in the Table V. Compared with the good outcome group, patients in the poor outcome group were more often female (52.2% versus 30.2%, p=0.0019). Distribution of stroke subtype showed that atherothrombotic and cardioembolic types were more frequent and lacunar type was less frequent in poor outcome group. Style of daily life, living alone or living with family, provided no significant influence on outcome. NIHSS score on admission was higher in poor outcome group than good outcome group ($p<0.0001$). Days of hospital stay were longer in the poor outcome group ($p<0.0001$). Previous stroke was higher in the poor outcome group ($p<0.04$). No significant difference was identified in other risk factors. Analysis of cognitive impairment showed that it was frequently observed in the poor outcome group.

DISCUSSION

In studies about acute stroke in older patients performed in other countries, the definition of older patients was not in concordance or unified. Some studies have examined patients aged 65 years and older (14, 26), or those aged 70 years and older (31, 24, 32), or those aged 80 years and older (27, 19, 25, 20). Currently, a few studies were

underwent about acute stroke in oldest old patients as 85 years and older (5, 23, 6), or aged 90 years and more (29). In this study, definition of older group as 75 years and more was referred from the late-stage medical care system for the elderly established in Japanese Government.

Differences in profile of risk factors for stroke were demonstrated between old patients and young patients. Patients in the older group more frequently had atrial fibrillation and history of previous stroke. On the other hand, the older group less often had hypertension, diabetes mellitus, hyperlipidemia and smoking habit. The results are in good agreement with previous studies in Europe (19, 6), South America (27), Caribbean (23) and Asia (17). It might reflect selective survival of older patients and between- generation differences in lifestyle (17) and recent westernized life style in Japanese younger generations. In laboratory data, serum total cholesterol, serum triglycerides, were significantly higher , and serum HDL cholesterol tended to be higher in the younger group. The results are similar with previous studies, thus Hayashi et al. showed that lower HDL cholesterol was an significant risk factor for stroke, especially in diabetic older patients (11) . Ness et al. showed that high serum LDL cholesterol was a significant independent risk factor of ischemic stroke in older men and women, and low serum HDL cholesterol was a significant predictor for the stroke in older women (22).

No significant difference in stroke subtype was revealed between the two age groups. Cardioembolic type was the most common in both the aged and younger patients in this study, which is inconsistent with previous studies performed in Asian countries (17, 20). Possible explanation for the inconsistence might be nature of our institute that has been specialized in cardiovascular diseases as well as cerebrovascular diseases, leading to increased number of younger group patients.

Older patients showed more severe symptoms on admission and poorer outcomes than younger patient. Poor outcome was attribute to clinical features including female sex, previous stroke, cardioembolic type and severe symptoms on admission. Kimura *et al*. showed that female sex, advanced age, atrial fibrillation and history of stroke were independent factors associated with severity in stroke (15). Previous studies aimed at gender difference in acute ischemic stroke showed that female patients had poorer prognosis than male patients (7, 28, 8, 12). Alkayed *et al*. showed that endogenious estrogen improves stroke outcome during vascular occlusion by exerting both neuroprotective and flow-preserving effects (3). After menopause, a rapid increase in frequency and severity of cerebral atherosclerosis and cerebrovascular events has been demonstrated in women, which might be due to estrogen alternation of lipid metabolism (9). Several studies showed patients in the older group more frequently had atrial fibrillation (17, 19 ,24, 26, 27). Our study comfirmed again that oral anticoagulation with warfarin is indicated for primary and secondary prevention of stroke in patients $\geqq$60 years old with atrial fibrillation (10). Insufficient warfarinization might be due to complexity of the management, however, adequate anticoagulation therapy is a prerequisite for stroke prevention in old patients with atrial fibrillation.

In conclusion, our investigation demonstrated that clinical phenotype and outcome in stroke in Japan have been modified. Further accumulation of re-evaluation of risks will contribute to prevention of stroke in the old-old adults and eventually reduction of medical cost in Japanese longevity society.

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