Young Adult Stroke in Taiwan: etiologies and outcomes

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Abstract

Background Early-onset adult stroke has not been fully characterized in Asians. **Objectives** We investigated the etiologic subtypes, risk factors and 1-year outcomes of early-onset stroke (16 – 55 years of age) in a Taiwanese cohort. **Methods** We retrospectively reviewed consecutive patients with acute stroke admitted to the Taipei Veterans General Hospital in Taiwan between 2009 and 2017. Patients were classified by age of onset ($\leq$ or $>$ 55) and etiologic subtypes and regularly followed for 1 year. **Results** Among all stroke patients (n=8155), 17.6% (n=1310) were early-onset, who had slightly more spontaneous hemorrhagic stroke (50.8%) than ischemic stroke (49.2%). The most common etiologic subtypes of hemorrhagic stroke were hypertensive intracerebral hemorrhage (ICH), subarachnoid hemorrhage and undetermined ICH. The most common subtypes of infarction were large artery atherosclerosis, other determined diseases (52.5% arterial dissection) and embolic stroke of undetermined source. Smoking, alcohol overdrink, obesity, ischemic heart disease and family history of stroke were more in the early-onset than the elderly patients. The early-onset patients with familial stroke (n=87, 6.6%) were more males and more commonly had infarction than those without familial stroke. Monogenic diseases accounted for 5.7% of young familial stroke. At 1-year follow-up, the early-onset patients with infarction displayed greater functional improvements but more stroke recurrence than those with ICH. **Conclusions** Hypertensive hemorrhagic stroke and large artery atherosclerosis or dissection occlusion are characteristically common etiologies of young stroke in Taiwan. Early-onset infarction had higher recurrence yet better 1-year outcomes than early-onset ICH. Patients with familial versus non-familial aggregation had more ischemic infarction and monogenic diseases.

Background

Stroke incidence in young adults has been rising worldwide possibly due to an increasing incidence of risk factors [1-4]. Overall incidence rates under the age of 55 have been reported to range from 7 to 15 in 100,000 person/year, with higher rates reported in American blacks, Japanese, Libyans and Hispanics, particularly in the age range of 35 – 55 years old [5]. Young stroke patients have a greater socioeconomic burden due to long-term disability and healthcare costs, so understanding the risk factors, etiologies and outcomes to prevent stroke is particularly important. The prognosis of early-onset stroke seems favorable as compared with older stroke patients, but excess mortality is present across all age groups of patients under 50 years in a Dutch study [6, 7]. Two large consecutive series from Finland and Netherlands reported a nonnegligible cumulative risk of recurrence in early-onset stroke survivors, ranging from 9.4% at five years to 19.4% at 20 years, respectively.[8, 9]

Among the constellation of risk factors, a family history of stroke has been identified as an independent risk factor for both hemorrhagic and ischemic strokes [10-13], and two case-control studies have demonstrated that a positive family history of stroke was related to increased risk of hemorrhagic stroke and ischemic stroke among young adults [14, 15]. The prevalence of family history among young stroke patients ranged from 5.5 to 48.7% [16, 17]. A prospective hospital-based study reported that family history of stroke was present in 37.3% of young European patients with stroke, and female probands with

a family history more often reported stroke in the maternal lineage [18]. However, whether there is an association between family history and specific stroke subtypes remains unclear [14, 15].

The etiologic subtypes and prognosis of stroke were different in the Asian population than the Western population. Hemorrhagic stroke was found to be more common in Asian patients than Caucasian patients [19, 20], and different risk factor distributions were proposed to account for the different distributions of pathological types of stroke [21]. For example, hypertension and alcohol were more prevalent in intracerebral hemorrhage (ICH) than infarction in Chinese but not white patients [21]. However, with regard to patients with early-onset stroke [22], the data in Taiwan were scarce. Here, we characterized etiologic subtypes, risk factors (including a family history of stroke) and 1-year outcomes of young Taiwanese stroke patients.

Methods

Stroke registry

We retrospectively reviewed the Stroke Registry of Taipei Veterans General Hospital, which included all patients of acute stroke admitted to the hospital between February 1, 2009 and June 30, 2017. Two specialized nurses were responsible for data registry as well as regular follow-ups of patient functional outcomes (modified Rankin scale, mRS) at 1, 3, 6, and 12 months after stroke by visits or phone interviews. Collected data included demographic and risk factors, functional measures (National Institute of Health Stroke Scale, NIHSS, and mRS) at acute baseline and at discharge, stroke subtypes, and medical and interventional therapies. The Institutional Review Board has approved the study (2017-03-007AC).

Subjects and subtype classification

Patients with acute ischemic infarction (including cerebral venous thrombosis), spontaneous ICH and subarachnoid hemorrhage (SAH) were included. We excluded patients with transient ischemic attack to avoid diagnostic ambiguity. Ischemic infarction was classified according to The Trial of Org 10172 in Acute Ischemic Stroke (TOAST) into large artery atherosclerosis, small artery occlusion, cardioembolism, and other determined and undetermined causes [23]. Spontaneous ICH was classified into structural vascular lesions, medication, amyloid angiopathy, systemic diseases, hypertension, or undetermined causes, i.e., the SMASH-U system [24]. A positive family history of stroke was defined as at least 1 first-degree or second-degree family members having had a stroke. Alcohol overconsumption was defined as more than 14 drinks per week for more than 6 months before stroke onset. Smoking was defined as smoking at least 0.5 packs per day for more than 6 months before stroke onset. Obesity was defined as a body mass index > 30.

The diagnostic algorithm for ischemic and hemorrhagic stroke is illustrated in Figure 1. The brain computed tomography (CT) and magnetic resonance imaging (MRI) determined ischemic or hemorrhagic stroke. For stroke subtyping, contrast-enhanced CT or MR angiography of the brain and neck, extra- and

intracranial doppler ultrasound, 24-h Holter, transthoracic cardiac echogram, coagulation profile, autoimmune profile, tumor markers, and homocysteine further categorized the events by the TOAST system. For advanced investigation, thin (1 mm)-section contrast-enhanced MR was reserved for patients suspected to have intracranial arterial dissection. Digital subtraction angiography was reserved for patients with intracranial vascular anomalies, such as Moyamoya disease, arteriovenous malformation and aneurysms. Transesophageal echocardiography was reserved for patients with suspected patent foramen ovale or cardioembolism without evidence of atrial fibrillation on 24-h Holter recording. Toxicology screening, cerebrospinal fluid studies and genetic studies were done in selective young patients if there was suspicion of illicit drug use, infections of the central nervous system, or monogenic stroke diseases, such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome, Fabry's disease, and hyperhomocysteinemia. Cryptogenic strokes were followed for re-subtyping (if specific cause was identified) by the end of the study period.

Statistics

Patients classified as having early-onset versus late-onset stroke, ischemic versus hemorrhagic stroke, and presence versus absence of familial stroke were compared by the 2-sample independent t test, and proportions were compared by the χ^2 test. Two-way analysis of variance (ANOVA) was performed to identify whether there was an interaction between age and stroke type (ischemic or hemorrhagic) on 1-year change of mRS. Binary multivariate logistic regression analyses were performed with stroke recurrence or favorable outcome at 1 year as the dependent variable and documented vascular factors and stroke subtype as the independent variables. Documented vascular factors were: male, hypertension, diabetes, atrial fibrillation, ischemic heart disease, peripheral arterial disease, history of previous transient ischemic attack (TIA) or stroke, and smoking [25]. Statistical significance was set at $p < 0.05$.

Results

Stroke subtypes

After excluding patients with duplicate registration, there were 8155 consecutive patients; 1310 patients (17.6%) were ≤ 55 years old and 6845 patients were > 55 years old. The mean age for the early-onset group was 45.9 ± 8.3 years, and there were significantly more males than females (male/female ratio 1.9:1). The early-onset patients had a higher percentage of hemorrhagic stroke (50.8%) than ischemic stroke (49.2%, Figure 2A). Of hemorrhagic stroke, hypertensive ICH, SAH and undetermined ICH represented 85.0% of the patients (36.2%, 30.2% and 18.8%, respectively) (Figure 2B). Regarding ICH, the top causes were hypertensive ICH (51.8%), undetermined (26.9%), and structural angiopathy (15.9%). Specifically, most of the structural angiopathy was arteriovenous malformation (59.5%), followed by cavernoma (23.0%) and aneurysm (8.1%). Regarding infarction, large artery atherosclerosis as well as other determined and undetermined etiologies were the top 3 subtypes, accounting for 32.6%, 21.7% and 20.2% of all ischemic infarctions, respectively (Figure 2C). Among the other determined etiologies, arterial

dissection (n = 73, 52.1%, table 1), Moyamoya disease (7.1%), cerebral venous thrombosis (7.1%) and anti-phospholipid syndrome (5.7%) were the most common causes (Table 1). Importantly, 9 patients (6.4%) had a monogenic cause (Table 1).

Risk factors

Figure 3A lists the differences in risk factor frequencies between the early-onset and late-onset stroke patients. For infarction, hypertension was the leading risk factor in both early-onset and late-onset patients (52.5% and 77.2%, respectively) and was more frequent in the late-onset patients ($\chi^2 = 181.6$, $p < 0.001$). Diabetes, ischemic heart diseases and atrial fibrillation were also more common in the late-onset patients (diabetes, late-onset 36.8% vs early-onset 27.8%, $\chi^2 = 20.2$, $p < 0.001$; ischemic heart diseases, late-onset 16.8% vs early-onset 6.7%, $\chi^2 = 44.4$, $p < 0.001$; atrial fibrillation, late-onset 20.4% vs early-onset 3.4%, $\chi^2 = 109.5$, $p < 0.001$). In contrast, 41.8% of the early-onset patients with infarction were smokers, 27.6% were alcoholics, 11.3% were obese, and 9.6% had a positive family history of stroke, which were significantly higher than the ratios in the late-onset patients (22.0%, $\chi^2 = 120.6$, $p < 0.001$; 14.9%, $\chi^2 = 68.5$, $p < 0.001$; 5.0%, $\chi^2 = 20.8$, $p < 0.001$; 3.7%, $\chi^2 = 46.3$, $p < 0.001$; respectively).

Regarding ICH, hypertension was also the most common risk factor in both the early- and late-onset patients, with a higher frequency in the late-onset patients (72.7% vs 55.3%, $\chi^2 = 46.4$, $p < 0.001$). Similarly, a higher proportion of the late-onset patients had diabetes (23.2% vs 11.6%, $\chi^2 = 29.7$, $p < 0.001$), ischemic heart diseases (11.9% vs 3.4%, $\chi^2 = 27.2$, $p < 0.001$) and atrial fibrillation (8.7% vs 1.1%, $\chi^2 = 31.7$, $p < 0.001$). Nevertheless, more early-onset patients were smokers (39.4% vs 24.8%, $\chi^2 = 35.5$, $p < 0.001$), alcoholics (35.3% vs 21.5%, $\chi^2 = 31.9$, $p < 0.001$), obese (14.2% vs 4.7%, $\chi^2 = 41.7$, $p < 0.001$), and had a family history of stroke (4.5% vs 2.5%, $\chi^2 = 5.3$, $p < 0.05$).

Family history of stroke

Comparing early-onset patients with and without a family history of stroke (n=87 versus 1223, Table 2), we noted that familial stroke patients were more commonly male. Infarction was significantly more common in patients with familial stroke, whereas SAH was significantly more common in patients without familial stroke. The subtypes of infarction and ICH, however, did not differ between groups. However, monogenic causes of infarction were significantly more prevalent in familial stroke. The stroke risk factors, including hypertension, diabetes, obesity, alcohol overconsumption and smoking, also made up similar proportions between groups. Among familial stroke patients, a greater percentage had hypercholesterolemia and ischemic heart disease. The 1-year stroke recurrence rate was significantly higher in familial stroke than in non-familial stroke patients, whereas the 1-year outcomes in mRS were lower in familial stroke.

Outcomes

A total of 7590 (93.1%) patients completed the 1-year follow-up. In the young patients (n = 1280), 76.8% of patients with infarction had favorable outcomes (mRS = 0 – 2) at 1 year after stroke, whereas only

52.7% of patients with ICH had favorable outcomes ($p < 0.001$). In the old patients ($n = 5988$), the proportions of patients with favorable outcomes at 1 year were lower for both infarction and ICH, but patients with infarction remained more likely to have favorable outcomes (48.5% vs 29.7%, $p < 0.001$). Two-way ANOVA revealed a significant main effect of age ($F = 113.6$, $p < 0.001$) on the 1-year changes of mRS, and there was no interaction between stroke type and age ($F = 1.7$, $p = 0.20$). Regardless of hemorrhagic versus ischemic stroke type, young patients still showed greater improvement in mRS score (-1.0 ± 0.05 vs -0.5 ± 0.03 , Figure 3C). The one-year mortality rate was higher after ICH than after infarction for both the young and the old patients (young: ICH 18.0% vs infarction 7.1%, $\chi^2 = 29.0$, $p < 0.001$; old: ICH 31.5% vs infarction 16.7%, $\chi^2 = 113.2$, $p < 0.001$). The predictors for favorable outcomes in the young patients were the absence of diabetes ($p = 0.003$), absence of a previous history of stroke or TIA ($p = 0.007$), and lower mRS scores at 3 months after stroke ($p < 0.001$).

In early-onset stroke patients, logistic regression found that after adjustments for covariates (age, NIHSS score at admission and counts of documented vascular risk factors), infarction type ($p = 0.005$) but not hemorrhagic type predicted stroke recurrence. Among the young patients, the stroke recurrence rate at 1 year was higher after infarction (3.6%) than after ICH (0.5%, $\chi^2 = 11.0$, $p = 0.001$). Of the 24 young patients with recurrent stroke within 1 year, 21 had infarction, 2 had ICH and 1 had SAH as the first stroke. Of the 21 patients with an initial infarction, 18 (85.7%) had recurrent ischemic infarction, and 3 (14.3%) had unknown subtypes of stroke. Of the 2 patients with an initial ICH, 1 had recurrent ICH, and the other had recurrent infarction. The patient with SAH had recurrent SAH as well.

Discussion

Hemorrhagic stroke is slightly more common than ischemic stroke in young Taiwanese patients. The most common subtypes of hemorrhagic stroke were hypertensive ICH and SAH, whereas the most common subtypes of ischemic stroke were large artery atherosclerosis and other determined infarction such as arterial dissection. Risk factors of smoking, alcohol overconsumption, obesity and a positive family history of stroke were more common in young patients. In the young patients with family history of stroke, there was a greater proportion of males, ischemic stroke, hypercholesterolemia, heart diseases and stroke recurrence at 1 year. At 1 year after stroke, young patients, particularly those with ischemic stroke, displayed greater improvements in mRS and lower mortality rate than old patients. Favorable outcomes in early-onset patients were predicted by absence of diabetes, absence of any previous stroke or TIA and a lower mRS score at 3 months after stroke. Our findings provide the characteristic etiologies and outcomes of young adult stroke in Taiwan. Recurrent stroke in early-onset patients was predicted by infarction type and male.

Young Asians present a greater incidence of hemorrhagic stroke, ranging from 20-40%, than western populations [22]. We found a higher proportion of hemorrhagic stroke (50.8%) than that previously reported by Asian studies, which was similar to the proportion reported in young west Africans (52.5%) [26]. In our ICH patients, hypertensive angiopathy was more common than structural angiopathies such as arteriovenous malformations, which was concordant with a previous Taiwanese report [27, 28]. This

observation was different from that found in a Korean cohort, in which vascular lesions were more prevalent than hypertensive angiopathy [29]. Genetic as well as non-genetic risk factors may contribute to such differences and need further investigation [21]. Regarding ischemic stroke, previous Asian studies reported that the subtype proportion of large artery atherosclerosis ranged from 7.5% to 35.4%, while small artery occlusion ranged from 17.4% to 42.5% [30, 31]. The prevalence of both subtypes of our patients fell within the reported range. Importantly, in our patients, the second most common infarction was other determined diseases, specifically arterial dissection (11.5%), which occurred more frequently than in other reported Asian cohorts [30]. This highlights the necessity of contrast-enhanced vessel wall imaging for suspicious dissection in young Asian patients.

Family history in early-onset patients with stroke has been suggested to have genetic predisposition and to be associated with certain ischemic stroke subtypes, including large artery atherosclerosis and small vessel occlusion predominantly in individuals aged below 65-70 years [13, 32]. A study in European young stroke patients, however, did not find such subtype correlation [18]. Despite the fact that Asian patients are known to have larger artery atherosclerosis and small vessel occlusion [33, 34], we did not find a difference in subtype distribution between familial and non-familial young stroke. Nonetheless, we found that ischemic stroke in total was more common than hemorrhagic stroke in familial young stroke. This may be explained by the small sample size and high prevalence of conventional vascular risk factors (87.8%) in familial young stroke, thus suggesting the complex gene-environment interactions in individual subtypes. Indeed, the familial aggregation of vascular risk factors has also been observed in stroke patients worldwide [35]. Nevertheless, consistent with a previous Spanish case-control study, our study showed that ICH was not significantly associated with family history of stroke [36].

Few studies of long-term outcomes have been conducted on stroke in young Asians. Regarding ischemic stroke, the proportion of unfavorable functional outcome (mRS = 3 – 6) in young patients was generally less than 20% [37, 38]. An ischemic stroke study in young Chinese individuals showed that poor outcomes at discharge were associated with certain stroke subtypes (large artery atherosclerosis and cardioembolism) and baseline NIHSS scores [39]. The Zurich and Bern ischemic stroke registries, as well as the Swiss Young Stroke Study and the Israeli young stroke registry, found that initial stroke severity and diabetes were associated with unfavorable outcomes or death at 3 months after onset [40-42]. Regarding ICH, a Finnish study reported a poor long-term (a mean of 9.7 years) unfavorable outcome as high as 49%, which was associated with age, initial stroke severity and intraventricular hemorrhage [43]. In our patients, the independent predictors for 1-year favorable outcome (mRS = 0 – 2) were absence of diabetes or previous stroke history and low mRS scores (0 – 2) at 1 month after stroke, including infarction and ICH.

Regarding stroke recurrence, Increasing counts of vascular risk factors have been shown to be independently associated with long term mortality [8, 25, 44, 45]. Of the ischemic stroke subtypes, large artery atherosclerosis carries the highest risk for mortality [25], and large-artery atherosclerosis, cardioembolism, and small-vessel occlusion are more likely to recur than undetermined and other determined causes [8, 9]. We finding reports that infarction is more likely to recur than ICH, and male sex,

which has been considered a documented non-modifiable risk factor, is an independent predictor. However, we did not find any difference between subtypes of infarction, possibly due to the limited duration of follow-up of our study (one year).

There were several limitations to our study. First, this was a single-center registry that may not be representative of the national population. Second, there were possibly incomplete details in this retrospective study of the cohort database, such as stroke subtype and family history of stroke. Thus, additional follow-ups of complete pedigrees of familial stroke patients are warranted. Third, although we identified a few monogenic stroke diseases, the genetic diagnosis of rare hereditary diseases is challenging and usually underestimated since it was only applied to selected patients with classic characteristics. A genetic screening may be considered in early-onset patients with a family history of stroke.

Abbreviations

ANOVA, analysis of variance; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CT, computed tomography; CVT, cerebral venous thrombosis; ICH, intracerebral hemorrhage; MELAS, mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes syndrome; MRI, magnetic resonance imaging; mRS, modified Rankin scale; NIHSS, National Institute of Health Stroke Scale; SAH, subarachnoid hemorrhage; SD, standard deviation; SMASH-U, structural vascular lesions, medication, amyloid angiopathy, systemic diseases, hypertension, or undetermined causes; TOAST, Trial of Org 10172 in Acute Ischemic Stroke; TIA, transient ischemic attack.

Declarations

Ethics approval and consent to participate

Data were obtained from the Stroke Registry of Taipei Veterans General Hospital, so there was no need for consent of the subjects. The study was approved by the Taipei Veterans General Hospital Institutional Review Board (2017-03-007AC).

Consent for publication

Not applicable.

Availability of data and material

The data that support the findings of this study are available from Taipei Veterans General Hospital but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Taipei Veterans General Hospital.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

CC analyzed and interpreted the data, and drafted the work. PL, RS, SH and YW analyzed the data. JT, HH and TL had a major contribution to collecting the data. CL, CT, LH, CC, HL and NC provided advices to the analysis and interpretation of the data. IL made substantial contributions to the conception and design of the study and substantially revised the manuscript. All authors read and approved the final manuscript.

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Tables

Table 1. Causes of young ischemic stroke of other determined etiologies

Diseases	Number of patients (n = 140)
Arterial dissection	73
Autoimmune disease	13
Antiphospholipid syndrome	8
Systemic lupus erythematosus	5
Moyamoya disease	10
Cerebral venous thrombosis	10
Cancer-related stroke	7
Monogenic disease	10
CADASIL	5
CADASIL2	1
MELAS	3
Fabry's disease	1
Hematologic disease	4
Thrombocytosis or polycythemia vera	2
Protein C or protein S deficiency	2
Amphetamine overuse	2
Others	11

Others: cryptococcal meningitis, arteriovenous malformation, reversible cerebral vasoconstriction syndrome, post-carotid stenting, fibrinoid strands, syphilis, hyperhomocysteinemia

CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; MELAS, mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke

Table 2. Characteristics of early-onset stroke with and without family history

	Family history (n = 87)	No family history (n = 1223)	P
Age	46.9 ± 7.4	45.8 ± 8.4	0.13
Gender (male)	68 (78.2%)	793 (64.8%)	0.011
Total	65 (74.7%)	579 (47.3%)	< 0.001
ICH	21 (24.1%)	444 (36.3%)	0.021
SAH	1 (1.1%)	200 (16.4%)	< 0.001
Monogenic diseases	5 (5.7%)	5 (0.4%)	< 0.001
Hypertension	41 (47.1%)	635 (51.9%)	0.39
Diabetes	16 (18.4%)	221 (18.1%)	0.94
Hyperlipidemia	33 (37.9%)	275 (22.5%)	0.001
Ischemic heart diseases	9 (10.3%)	53 (4.3%)	0.011
1-year stroke recurrence	4 (4.6%)	20 (1.6%)	0.047
One-year outcomes in mRS	1.3 ± 1.8	1.9 ± 2.2	0.014

ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage.

Figures

Figure 1

Diagnostic algorithm and classification of etiological subtypes in young stroke patients. CTA, computed tomography angiography; DSA, digital subtraction angiography; MRA, magnetic resonance angiography; TCD, transcranial doppler ultrasound; SAH, subarachnoid hemorrhage.

Figure 2

Distribution of stroke subtypes in early-onset patients. A. Pie chart for all etiologies of ischemic and hemorrhagic stroke. B. Frequency of hemorrhagic stroke. C. Frequency of ischemic stroke. C, cardioembolism; Hyp, hypertension; L, large artery atherosclerosis; Med, medication; O, other determined; S, small artery occlusion; SAH, subarachnoid hemorrhage; Str, structural angiopathy; Sys, systemic disease; U, undetermined.

Figure 3

A. Frequency of risk factors in patients with infarction. B. Frequency of risk factors in patients with intracerebral hemorrhage. C. The modified Rankin scale scores at different time points of follow-up (1, 3, 6 and 12 months) for young and old patients with infarction or ICH. D. The 1-year mortality for young and old patients with infarction or ICH. E. The 1-year recurrence for young and old patients with infarction or ICH. * $p < 0.05$, *** $P < 0.001$, vs. old patients. † $p < 0.05$, †† $p < 0.01$, ††† $p < 0.001$, vs infarction.