Research Article

Hospital based study in assessment of risk factors of stroke in young adults.

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Abstract
Background: Stroke is often considered a disease of older people, but an estimated 10% of patients with stroke are younger than 45 years. There is an evidence that the incidence of ischemic stroke in young adults is rising, although the reasons for that increase are unclear. **Patients and Methods**: We studied patients with acute ischemic stroke or transient ischemic attack who were admitted in the stroke unit –Neurology department, Kasr-Alainy hospital within the first week of acute event. The study was carried out during the period between December 2018 and December 2019. **Results**: Analysis was done for 70 ischemic stroke patients from urban and from rural area. Onset to door was shorter in urban. Urban patients showed an older age and higher prevalence of hypertension and diabetes (65.9%, 48.6% respectively), while rural patients were characterized by female preponderance (51.5%), more dyslipidemia, smoking 44.6%, stroke in young 20.5%, atrial fibrillation 23.8% % and recurrent stroke 44.3%. Rural cases showed a severer deficit at onset and poorer outcome. **Conclusion**: Vascular risk factors, stroke type, and presentation tend to differ in Egypt according to the geographic distribution whether urban or rural. Studying patterns of such difference may aid in planning specific targeted preventive and therapeutic strategies for stroke in urban and rural Egypt.
Keywords: Stroke, young adults, rural area

Introduction
Stroke is the third most common cause of disability and second most common cause of death worldwide. Although more common in older adults, stroke also occurs in neonates, infants, children, and young adults, resulting in significant morbidity and mortality.

Approximately 80% of all strokes are ischaemic strokes, of which roughly 10% occur in individuals under the age of 45 years—so-called 'young stroke'

Worldwide, more than two million young adults have an ischaemic stroke yearly. Stroke in young adults has a considerable socioeconomic impact because of high health-care costs and loss of labour productivity.
A greater proportion of strokes are due to subarachnoid haemorrhage and intracranial haemorrhage in young adults (40–55%) compared to the general stroke population (15–20%), cerebral infarction is still most common.

In young adults with stroke, data on causes and risk factors come from just few centers or population-based cohorts. Cardioembolic stroke is more common among younger patients. Other conditions associated with ischemic stroke include vasculopathy (such as arterial dissection), cardiac defects, recent pregnancy, other hypercoagulable states, smoking, illicit drug use, premature atherosclerosis, hypertension, and possibly migraine. Patients come complaining of various neurological deficits affecting motor, sensory, coordination or sphincteric systems. Furthermore, prognosis after stroke differs in patients with a life expectancy of decades, in comparison with older patients.

Investigations into the cause of ischaemic stroke at a young age often pose challenges. By contrast to stroke in older patients, many different, often rare, causes and risk factors are associated with stroke at a young age, including illicit drug use, prenancy, arterial dissections, and patent foramen ovale (PFO), which require specific additional investigations and treatment.

Stroke in the young requires a different approach to investigation and management than stroke in the elderly given differences in the relative frequencies of possible underlying causes. It remains the case, however, that atherosclerosis contributes to a large proportion of stroke in young patients, thus, conventional risk factors must be targeted aggressively.

Neurosonology helps in diagnosis and peri-interventional assesment of Carotid Artery disease in Patients who undergo carotid revascularization procedures. It is safe, low cost, bed side, noninvasive but operator dependent.
Cervical duplex ultrasound can directly visualize atherosclerotic plaques, detect the Degree of stenosis, near total occlusion and complete occlusion of Carotid artery and differentiate between acute and chronic occlusion to detect need for end arterctomy.

Also it can detect vertebral stenosis, intra luminal thrombus in Cervical vessels, subclavian steel phenomenon and other uncommon causes of stroke such as Cervical artery dissection, fibromuscular dysplasia, aortic arch dissection.

Trans cranial doppler or trans cranial colour coded duplex sonography helps in detection of occlusion or stenosis, confirmation of vascular origin of the presenting symptoms, mapping of the collateral circulation, detection of microemboli and right to left shunt.

Patients

Patients who will be admitted in the stroke unit – Neurology department, Kasr Alainy hospital within the first week of the acute event from December 2018 to December 2019.

Patients fulfilling inclusion criteria will be planned for full clinical assessment including general and neurological examination, laboratory investigations and imaging for risk factor assessment.

Inclusion criteria:

1. Age older than 18 and younger than 40 years old
2. Both sexes.
3. Diagnosis of acute arterial cerebral ischemic event or transient ischemic attack. It was based on both clinical assessment and cerebral imaging (a brain CT scan or MRI). According to the most recent definition of stroke for clinical trials. It had required either focal neurological deficit lasting >24 hours or imaging of an acute clinically relevant brain lesion in patients with rapidly vanishing symptoms.
4. Presentation within one week from the acute event.

Exclusion criteria:

Subjects were excluded if:

1. Age: younger than 18 and older than 40 years old.
2. Presented with cerebral hemorrhage, subarachnoid, venous sinus thrombosis, focal brain lesion or demyelinating lesion.

METHODS

A- Clinical Assessment:
For the patients including:

- Full history will be obtained by interviewing the patients (if applicable) and/or their relatives, focusing on risk factors, presence of comorbidities, time laps between the event and admission, and neurological symptoms (according to a previously prepared sheet).
- General examination to assess vital signs (esp. Blood pressure) and other systems was carried out.
- Neurological examination and assessment of stroke severity using National Institute of Health system score (NIHSS) *respectively* .
- Electrocardiogram (ECG) to assess any cardiac rhythm abnormality or abnormal wave morphology.

B- Laboratory Assessment for both patients include:

- Complete Blood Count (CBC) and Erythrocyte Sedimentation Rate (ESR), kidney and liver functions, electrolytes (Na, K, and Ca), lipid profile and International Normalized Ratio (INR), fasting blood sugar (FBS) and 2 hours post prandial, Uric acid.
- Some patients will do further laboratory studies if diagnosis is not reached via routine studies such as vasculitic profile and work up for high coagulable state.

C- Imaging Assessment:

1- Brain imaging: Brain computed tomography (Brain CT) was carried out on admission for all studied patients. Axial CT cuts were performed while patients were lying in the supine position with 15-20 degree tilt with 1cm slice thickness in addition to posterior fossa cuts every 0.5cm. CT brain was performed to confirm the presence of cerebral infarction and to exclude hemorrhage or old ischemic events .Some patients will do brain MRI if the diagnosis is not clear.

2- Cardiovascular imaging: Carotid and vertebrobasilar duplex and Doppler studies were performed at the Neurosonology unit, department of neurology Cairo University using Phillips HDI 5000 ultrasound equip-ment (Phillips Corporation, Netherland, 2009) to assess the common carotid artery, internal carotid artery, vertebral and basilar arteries (Extracranial assessment), middle cerebral artery, anterior cerebral artery, posterior cerebral artery, distal internal carotid artery, vertebral and basilar arteries (Transcranial assessment) . Evaluation will be done of intima media thickness (IMT), the presence of atherosclerosis or arterial dissection, peak systolic velocity, end diastolic velocity and resistive index.

3- Transthoracic echocardiography was performed while the subject in the left lateral position using Phillips S72 Omni ultrasound equipment (Phillips Corporation, Netherland, 2006). M-mode echocardiography was carried out to assess the chamber dimensions, valves state, ejection fraction and regional wall motion.

Statistical Analysis

Statistical analysis was done on a personal commuter using SPSS version 16th version Statistics (SPSS Inc., Chicago). The Kolmogorov-Smirnov goodness of fit test was performed to test the normality of continuous data distribution. Continuous data were presented as mean and SD if normally distributed and as median and range for skewed data, whereas categorical data were presented as frequencies. Regarding bivariate analysis, Student t test was used to compare normally distributed continuous variable with nominal independent variable. Mann-Whitney.

U test used to compare not normally distributed continuous variable with nominal independent variable and to correlate ordinal dependent variable versus nominal comparison of nominal data. Fisher's exact test was used if more than 20% of the cells in any cross tabulation had an expected count of less than or equal to 5. P value less than 0.05 was considered statistically significant.

Results

A total of 70 patients with a newly diagnosed stroke were included in the study. There were 42 men (41.2%) and 60 women (58.89%). Mean age at onset was 35.7(±7.9 years) (range: 15-45 years). Incidence of infarct increased with age.

The age-specific incidences of stroke and stroke subtypes are shown in table 1. Ischemic stroke of other determined etiology (37.3%) was the most common subtype, whereas large-artery atherosclerosis was the least common etiology. Age was significantly lower in stroke of other determined etiology ($p<0.01$) and significantly higher in stroke of undetermined etiology ($p=0.01$).

A survey of the traditional risk factors revealed that smoking (31.4%), hypertension and diabetes mellitus (12.7% for

each one), and a family history of stroke (10.8%) were the most common. Ischemic stroke was reported during pregnancy and postpartum in 7 patients (6.9%). Of the potentially modifiable risk factors, alcohol misuse, dyslipidemia, migraine with aura, and the use of illicit drug were reported in 4, 3, 1, and 1 cases respectively. Seven patients (6.9%) were found to be in the large artery atherosclerosis category (TOAST 1):

There were 4 men and 3 women with a mean age of 40.5± 5.1 years. Six patients had more than 2 traditional risk factors: 4 patients were smokers, 3 patients were both hypertensive and diabetic and 2 patients were dyslipidemic. Only one patient had no risk factor but the diagnosis, made by carotid duplex imaging, showed a stenosis greater than 50% of the appropriate artery, with excluding potential sources of cardiogenic embolism. Twelve patients (11.8%) were classified in the“ cardioembolism” category (TOAST 2):

we reported 3 cases of dilated cardiomyopathy; 2 cases of infective endocarditis, 2 cases of atrial fibrillation, 2 cases of patent foramen ovale) PFO) associated with deep vein thrombosis, one single case of mitral valve prolapse, a case of intracardiac thrombus, and a case of mitral stenosis without atrial fibrillation.

Transesophageal echocardiography (TEE) was more sensitive than transthoracic echocardiography (TTE) to detecting some causes of cardioembolism: 1 patient with PFO had a normal TTE. Nine patients (8.8%) were classified in the “small-vessel occlusion” category (TOAST 3). The diagnosis was made by imaging evidence of small-vessel disease by MRI in cases and by CT scan in one single case.

Thirty eight patients (37.2%) were classified in the "other determined etiology" category (TOAST 4). In TOAST 4 category (table 2), the most common etiologies were antiphospholipid syndrome (36.84%), neuro -Behçet’s disease) 10 and Takayasu’s disease (7.89%). Among the 14 patients of the antiphospholipid syndrome group, 4 had systemic lupus erythematous. Thirty-six patients (35.3%) were classified in the "undetermined etiology" category (TOAST 5).

During the first month, we noted 8 cases of thromboembolic complications: six patients had deep vein thrombosis of the lower limbs and 2 had pulmonary embolism. Three patients died in the first 48 hours. These deaths were a consequence of pulmonary embolism in 2 cases and severe heart failure due to dilated cardiomyopathy in one case. After this month, 2 patients presented deep vein thrombosis of the lower limbs and 3 patients died on day 47, day 78 and one year later, respectively. The mean follow-up period was 30.5 months.
Moreover, during the follow-up period, 14 patients presented a recurrent stroke. Large artery atherosclerosis، atrial fibrillation and dilated cardiomyopathy were the leading causes of recurrent ischemic stroke.

Variable	Frequency	%
Age:		
18-30 years	11	15.7
30-40 years	59	84.3
Sex:		
Male	33	47.1
Female	37	52.9
Residence:		
Rural	45	64.3
Urban	25	35.7
Occupation:		
Unemployed	18	25.7
Housewife	33	47.1
Manual worker	5	7.1
Employee	14	20
Handedness		
Right handed	70	100

	Frequency	%
Brain imaging:		
Free	4	5.7
Territorial	58	82.9
Lacunar	7	11.4
Brain circulation: (65)		
Anterior	52	74.3
Posterior	13	18.6
Vascular imaging: (69)		
Normal	49	71.0
Atherosclerotic	10	14.4
Non atherosclerotic	10	14.4
Vascular imaging: **(extra cranial atherosclerosis)**(4)		5.7
Plaque	3	4.3
Complete occlusion	1	1.4
Vascular imaging:**(intra cranial atherosclerosis)** (4)		5.7
Stenosis	2	2.8
Complete occlusion	2	2.8
Vascular imaging: (combined extracranial and intra cranial atherosclerosis)	2	2.8
Vascular imaging**: (non atherosclerotic)** (10)		14.4
Thrombosis	2	2.8
Dissection	4	5.7
Other causes	4	5.7
ECHO: (69) Normal	32	45.7
LVH	14	20
Ischemic cardiomyopathy	4	5.7
Valve lesion	17	24.3
Mitral valve prolapse	2	2.9
TEE: (15)		
Normal	6	40
PFO	6	40
MVP	1	7
Intra-cardiac thrombus	2	13

Discussion

Although the overall stroke incidence has been declining, there is evidence that young ischemic stroke is increasing[1,2]. In the current study, we found that women out-numbered men (58.8 vs. 41.2%) with a male: female ratio of 0.7. Some previous studies reported similar results: Switzerland study[11] (sex ratio of 0.78) and Mexico study[15] (sex ratio of 0.8).

These findings were different from those from studies from Sweden[12], Taiwan[22], and Korea[21] where the sex ratios were 1.43, 2.49, and 3.03 respectively. The European 15 cities young ischemic stroke registry reported a higher stroke incidence among women compared with men in the range 18-34 years with a reverse in the range 35-49 years[23] .

Regarding the risk factors for ischemic stroke, our most common risk factors were current smoking (31.4%), hypertension (12.7%), diabetes (12.7%), and a family history of stroke.

Comparing with previous studies[24,25], our findings were similar to Helsinki[24] and sifap1[25] studies: the frequency of smoking, hypertension and diabetes were respectively 44%, 39%, and 10.3% in the Helsinki study and 55.5%, 46.6% and 10.3% respectively in the sifap1 study. Smoking was an important risk factor for cerebral infarction in young adults[26]. The risk increased with the duration[26] and dose of the exposure[27]. The large proportion of smokers among young adults with stroke in countries with a high prevalence of smokers[28], particularly in some developing countries, is of concern[29,30]. Unlike R. RENNA et al., who documented dyslipidemia as the most common risk factor (52.7%)[3], we report only 2.9% of dyslipidemic patients in our study. This difference may be explained by missing values for blood lipids in a large group of our patients. All these data concerning traditional risk factors may suggest that there are still many efforts to make for primary prevention of stroke in the young, by controlling the current risk factors.

Regarding stroke subtypes, large artery atherosclerosis and small- vessel occlusion were the least common (6.9% and 8.8% respectively), according to some previous reports[11,15]. In spite of the important prevalence of some traditional risk factors for ischemic stroke in our patients, Atherosclerosis related strokes were noted in only 15.7 % of all patients (6.9% in large artery atherosclerosis and 8.8% in small- vessel occlusion). This may presuppose that traditional risk factors are predisposing factors for ischemic events: they may boost the thrombotic risk caused by other conditions.

Cardioembolism accounted for 11.8% of all strokes in our study, in agreement with reports from Thailand (13%)[31], Canada (14%)[16], and the United States (14%)[17]. The causes of cardioembolism in our study were similar to those reported in other Asian and American ones[16,17,31]. The TOAST 4 category was the most common stroke subtype in our study, involving 37.2% of patients.

This result was in line with those reported in Switzerland (46%)[11], USA(44%)[17], Mexico (40%)[15], Brazil (34.9%)[14], Saudi Arabia (30%)[20], and Korea (26.8%)[21]. In our study, we noticed that age was significantly lower in TOAST 4 strokes, as reported in Taiwan study [22]. These findings may suggest that the rare and genetic etiologies of stroke predominating in the population under 35 become increasingly rare in the patients over 35.
In our study, antiphospholipid syndrome (APS), neuro Behçet's disease and Takayasu's disease were the leading causes of TOAST 4 strokes.

Antiphospholipid syndrome was also one of the most common causes of young ischemic stroke in Taiwan, Sweden and Thailand[22,12,31]. However, in Taiwan study there was no case of Takayasu's disease and only one case of neuro-Behçet's disease[22]. In fact, Behcet and Takayasu's disease are common in our country. Three cases of systemic lupus erythematous were

noticed in young Thaiwanese adults[22]. The higher prevalence of systemic disease, among TOAST 4 etiologies', in our study can be explained by recruitment bias: all patients enrolled in our study were recruited from different departments of internal medicine all over the country. Comparing with findings from previous studies[22,11,12,3,32], carotid arterial dissection was lower. In fact, patients with dissected carotid artery were admitted to and managed in neurology and neurosurgery departments. As for inherited deficiency of coagulation inhibitors, it was reported in 3 patients. Among them, 2 patients (5.1%) had low protein S and one patient (5%) had factor V Leiden mutation. The incidence of inherited deficiency of coagulation inhibitors varies up to 23% in different studies[33]. Our findings were consistent with most reports[34]. However, they were different from those of recent studies in Korea[21], Morocco[5], and Sweden[12] in which there were no or rare cases of inherited deficiency of coagulation inhibitors. As for factor V Leiden mutation, it was reported as the most common inherited coagulopathy associated with stroke[35]. A meta-analysis published in 2004, showed that statistically significant associations with ischemic stroke were identified only for factor V Leiden, but not for the other 3 deficits[36]. Taking into account the preceding findings, we think that young adults with ischemic stroke, especially with a family or/and personal history of thrombotic events without precipitating factors, should be screened for thrombophilia.

Given the importance of TOAST 4 stroke in our study, and in accordance with the conclusions of Arboix A et al., we highlight the better prognosis of this category and the need to distinguish it from other ischemic stroke subtypes which have a different treatment approach and outcome[37].

TOAST 5 category accounted for 35.3% of stroke etiologies' in our study. In previous reports, young ischemic stroke with undetermined etiology varied from 15% to almost 50%. However, it seems necessary to emphasize the fact that TOAST classification may lead to overrating the group of undetermined cause, since it includes patients with 2 or more potential causes.

(TOAST 5a), those with no evident cause despite complete investigation (TOAST 5b), and those with incomplete investigation (TOAST 5c). That's why, more accurate etiological subtyping of ischemic stroke, such as SSS-TOAST, ASCO[38], and ASCOD classifications should reduce the high rate of undetermined etiology group. Age was significantly higher in this group of patients. Because of missing data, it wasn't possible to define the 3 subgroups of TOAST 5 category in our study. Therefore the diagnosis of properly cryptogenetic stroke (TOAST 5b) could not be confirmed. In fact, a common mistake is to diagnose a cryptogenetic stroke in patients with incomplete or delayed investigation. This error is of great importance, particularly in the following conditions: anomalies which can resolve quickly such as an intra cardiac thrombus, or results of some biological tests such as antiphospholipid antibodies of which repeated assessment is needed.

In our study, wherein a low rate of recurrence and mortality was noted, the prognosis of young adult patients with ischemic stroke was more favorable than in the previous studies.

Some limitations should be acknowledged. Information was gathered retrospectively, so some data were missing. Data in our report come from patients' series, which are by design unrepresentative of the population. Furthermore, self-reported data such as illicit drug use and excessive alcohol intake are subject to reporter biases, since some patients tend to conceal this information because of the taboo nature of such subjects. As for the outcome, the short follow up period and the important number of patients lost to follow-up were other limitations of our study.

Studies with longer time of follow-up are needed to assess the long term rate of recurrence, of sequellae and of mortality. Since all patients were recruited from internal medicine departments, recruitment

bias to the TOAST 4 category group, particularly systemic diseases, was inevitable. So cardio embolism and carotid arterial dissection, as causes of stroke in young adults could be underestimated. Nevertheless, our study is the first study dealing with young ischemic stroke in Tunisia, and it is among the rare ones in North Africa {5}.

Conclusion

Young ischemic stroke often poses a real diagnostic challenge to physicians. In this category of patients, a myriad of etiologic possibilities arises. Our study details stroke subtypes in Tunisian young adults and shows the particular distribution of stroke etiologies' in Tunisia. Most studies were made in developed countries. Because of the difference in resource allocation strategies between developed and developping countries, more studies and guidelines dealing specifically with stroke in young adults in developing countries, especially in North Africa, would be welcome.

Considering the serious personal, familial, and socio economic consequences of young ischemic stroke, the time to decide whether or not stroke is an issue that should be on the governmental agenda in our country has passed. The time has come for action.

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