

Risk factors and subtypes of ischemic stroke in young patients: an observational study from a teaching hospital in Saudi Arabia

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Summary

Young adults are a key part of any society and the psychosocial and economic burden of any chronic or devastating disease in this particular group has significant consequences and impacts negatively on the development of the society as a whole. Although stroke in this age group is relatively rare, its consequences, in terms of lifelong dependence and disability, are substantial. Therefore, it is important to address this issue.

In this retrospective epidemiological study, we analyzed the medical records of young patients (aged 18-45 years) with a diagnosis of stroke during the study period (January 2014 - February 2018).

The study population numbered 85 patients, and a male predominance was observed (67:18). Hypertension was the commonest risk factor, present in 43 (50.6%), followed by dyslipidemia and diabetes mellitus, present in 37 (43.5%) and 30 (35.3%) respectively. Lacunar infarction (LI) was the commonest type of stroke, observed in 30.6%, followed by cardioembolic stroke (20%). Of the other determined causes, Sick cell disease was the most frequent etiology. Undetermined causes were less frequent in our study (15.6%) and the presence of multiple etiologies was the main reason for classifying patients in this group. Sick cell disease was more common than arterial dissection in our study.

In our cohort of patients, stroke risk factors and classification of stroke etiologies according to the Trial of Org 10172 in Acute Stroke (TOAST) criteria were found to be in accordance with the current literature. Slight discrepancies were observed in gender distribution and etiologies compared with other studies from Saudi Arabia and international studies, and these need to be examined further through prospective studies.

KEY WORDS: *cardio embolic, ischemic stroke, lacunar, other determined, undetermined, young stroke.*

Introduction

Reports of ischemic stroke in young patients (defined as stroke in patients younger than 45 years old) are relatively rare compared with those in the population older than 45 years (Kristensen et al., 1997). However, the rates reported by different Authors vary greatly, ranging from less than 5% to more than 10% (Bogousslavsky et al., 1988; Siqueira Neto et al., 1996). Stroke in young individuals as opposed to the elderly population is of particular significance as it is associated, worldwide, with significant socioeconomic loss, given that members of this particular population are in their productive period and, being younger, can be assumed to have more survival years ahead of them. This loss of productivity, as well as the longer period in which these individuals are likely to be dependent, has a significant negative impact on families as well as society. Additionally, the risk factors for stroke in this age group are also different and somewhat unique compared with the more conventional risk factors, i.e. diabetes, hypertension, dyslipidemia and cardiovascular diseases, that account for the majority of strokes in the older population. Hematological causes, vasculitis, Moya Moya syndrome, vascular dissections and drug abuse are, for example, in different proportions, the more common causes of stroke in younger patients (Kristensen et al., 1997; Siqueira Neto et al., 1996; Cerrato et al., 2004; Lee et al., 2002; Awada, 1994; Kwon et al., 2000; Khan, 2007; Barinagarrementeria et al., 1996; Varona et al., 2007; Luijckx et al., 1993). There is some evidence that etiologies also vary according to different geographical regions. A few hospital-based reports from the Arabian Peninsula have shown that stroke is more common in young patients in this area than in young Western patients, but the risk factors associated with each type of stroke are similar (Al Rajeh et al., 1991; Yacub et al., 1991; Awada et al., 1992). Despite the significant impact of young stroke, both on society and on families, data on etiologies and disease burden from most parts of the Kingdom of Saudi Arabia are still sparse. We set out to identify the major risk factors responsible for this devastating disorder in this particular group of patients.

Materials and methods

A retrospective chart review of the patients suffering from acute ischemic stroke admitted to our hospital from January 2014 to February 2018 was carried out. Ischemic stroke was defined as a sudden-onset focal neurologic deficit with imaging-confirmed cerebral infarction. Individuals with other causes of stroke, such as intracranial hemorrhage, subarachnoid hemorrhage, and cerebral venous thrombosis, were excluded from the

analysis. From the total population of stroke patients, those who had suffered an ischemic stroke and were in the age range of 18-45 years were enrolled. As a matter of protocol, all stroke patients admitted to the neurology wards underwent routine hematological and biochemistry tests (complete blood count, prothrombin time, activated partial thromboplastin time, C reactive protein, serum creatinine, blood glucose and lipid profile), chest X-rays, electrocardiography, and brain imaging, including computed tomography (CT) and/or magnetic resonance imaging (MRI) at admission. Additionally, the majority of patients underwent vascular imaging studies such as MR angiography or CT angiography or carotid ultrasound. Transthoracic echocardiography (TTE) was performed in the majority of the patients as a baseline test and transesophageal echocardiography (TEE) was done if there was strong suspicion of cardioembolic (CE) stroke and TTE was inconclusive. Thrombophilia work up was done in cases where the stroke etiology could not be explained by routine investigations. More specific diagnostic testing (e.g. vasculitis profile) was performed when deemed necessary by the treating neurologist. Conventional cerebral angiography was considered if the clinical scenario raised the suspicion of vasculitis. Patient case records were reviewed by a neurologist and data regarding each patient's demographic profile, clinical presentation, medical history (emphasis on risk factors), results of vascular imaging, biochemical profile, and other diagnostic tests were recorded in a structured proforma. Stroke subtyping, according to the Trial of Org 10172 in Acute Stroke (TOAST) criteria, was based on the information available at discharge. Diabetes mellitus (DM), hypertension, smoking, dyslipidemia, previous stroke or transient ischemic attack, migraine, atrial fibrillation, coronary artery disease, alcohol consumption and drug abuse were considered as risk factors. Etiological classifications were also analyzed by dividing the cohort into two age groups (18-35 years and 36-45 years), as well as by gender. The recorded data were statistically analyzed for the percentage and mean and standard deviation of all variables. SPSS version 22 for Windows was used for all the statistical analyses. Categorical variables were analyzed by Fisher exact test or χ^2 test and continuous variables using the Student t test for continuous variables. P values of <0.05 were considered statistically significant.

Results

Our study was designed to consider patients aged between 18 and 45 years of age. The 85 patients included in our cohort ranged in age from 21 to 45 years, and they had a mean age \pm standard deviation of 38.66 ± 5.28 years. Males were predominant, accounting for 79% of the sample (n=67), while only 21% (n=18) were females. The male to female ratio was 3.7:1

The majority of the stroke patients were Saudis (n=48, 56%); Indians were the next largest group (n=11), accounting for around 13% (n=11); nationality was not known in 11 (13%). Table I shows the frequencies, in our sample, of known risk factors and of stroke subtypes according to the TOAST classification.

The majority of the strokes (n=61, 72%) occurred in the anterior circulation, where the middle cerebral artery ter-

Table I - Vascular risk factors and stroke subtypes according to TOAST classification.

Risk factors	No. of patients (% of total) Total patients = 85
Hypertension	43 (50.6%)
Dyslipidemia	37 (43.5%)
Diabetes mellitus	30 (35.3%)
Ischemic heart disease	9 (10.6%)
Prior stroke	8 (9.4%)
Prior history of transient ischemic attacks	2 (2.4%)
Migraine	1 (1.2)
Smoking	18 (21.2%)
Drug abuse	5 (5.8%)
Sickle cell disease	4 (4.7%)
Alcohol abuse	2 (2.4%)
Valvular heart disease	3 (3.5%)
Atrial fibrillation	2 (2.4%)
Cardiomyopathy	3 (3.5%)
TOAST classification of ischemic stroke	
Lacunar infarction	26 (30.6%)
Large artery atherosclerosis	14 (16.5%)
Cardioembolic strokes	17 (20%)
Other determined causes	15 (17.6%)
Undetermined etiology	13 (15.3%)
Incomplete evaluation	1 (8%)
Multiple etiologies	12 (92%)

itory was the commonest site of infarction, while the posterior circulation was affected in 24 (28%) of the cases. Lacunar infarction (LI) was the commonest type of stroke in our analysis: LIs were recorded in 26 cases, with the basal ganglia found to be the site most frequently involved. Head CT was the commonest imaging modality used in the emergency setting. All 85 patients had baseline head CT, and initially 31 CT examinations did not reveal any acute abnormality. MRI was performed in 55 patients. Vascular imaging was available in the majority of the patients; most underwent CT angiography while MR angiography was performed in 28 patients, and two patients had a conventional four-vessel angiogram. Carotid ultrasound was done in 30 patients. Echocardiography data were available in 74 patients. Most of the patients underwent TTE 62 (71.7%), while TEE was done in 26 (30.5%). Some patients underwent TEE directly if the suspicion of CE stroke was very high from the beginning, while in most cases, TEE was done after TTE, if no other cause of stroke was evident and the clinical syndrome pointed to either CE or cryptogenic stroke. Work up for thrombophilia (both genetic and acquired) was done in 65 patients: complete in 28/65 patients and partial in the others. The main reason for not having this work up was either that the patient was already known to have the hypercoagulable state, or his/her stroke clearly seemed secondary to

some other etiology, clinically and radiologically proven or otherwise (large artery occlusion or CE etiology). Exploration of risk factors after dividing the cohort into two groups according to age (18-35 years and 36-45 years) showed hypertension to be more common in the group aged 36-45 years (p-value 0.021), while alcohol abuse was more common in younger age group (p-value 0.054). The 36-45 year olds had a significantly higher percentage of patients with lacunar stroke (Table II), as hypertension is the commonest cause of this type of stroke, but the difference did not reach statistical significance. Table III details the other determined etiologies: Sickle cell disease (SCD) was the commonest, followed by arterial dissection. When the data were analyzed according to gender, the mean ages of the male and female patients were found to be 38.66±5.5 and 37.8±4.5 years, respectively. Most of the vascular risk factors were more common in the males than in the females. Hypertension was found to be present in 44.7% of the male patients, while only 5.8% of the females had hypertension diagnosed as a premorbid risk factor, with a significant p-value of 0.021. Table IV also analyzes risk factors and TOAST stroke subtypes according to gender. The only risk factor that was more common in the females was SCD, which was present in three females and only one male, with a p-value of 0.029. Since hypertension and DM were both more common among males, lacunar strokes were more frequent in this subgroup (Table IV), while CE and large artery atherosclerosis (LAA) stroke were each more common in females, albeit without the differences reaching statistical significance.

Discussion

Our center is a tertiary referral center that, following the establishment of neurovascular services, is one of the few centers in the eastern region of Saudi Arabia where a round the clock service is available for acute stroke, providing intravenous thrombolysis and interventional procedures.

Although there is still no specific definition of “young stroke”, the vast majority of authors consider “stroke in the young” to pertain to individuals under 45 years of age. The majority of our patients (n=67, 79%) were males. Male predominance has been reported almost universally in other studies, albeit in varying proportions. A study from the Abha region of the KSA (Babtain et al., 2014) also reported a male predominance, corresponding to 65%, and other studies from different parts of the world including Korea (Lee et al., 2002), Taiwan (Kwon et al., 2000) and India (Dash et al., 2014), too, have shown a similarly high male predominance (75% from Korea and 5:1 ratio from India). Instead, a 2010 comparative study between Australia and Malaysia found this ratio to be just 1.5:1 and 1.4:1, respectively in these countries (Tan et al., 2010), and other studies from western regions have also failed to document such a marked gender difference (44% to 58.9%) (Barinagarmenteria et al., 1996; Williams et al., 1997; Chan et al., 2000; Carolei et al., 1993). Overall, a significantly higher male to female ratio has been found in eastern countries that have relatively poor educational and medical resources as compared with western or better developed eastern countries. This difference in gender is not entirely un-

Table II - Vascular risk factors and stroke subtypes in the two age groups.

Demographics	18-35 years n=23	36-45 years n=62	p-value
Sex			
Males	19	84	0.42
Females	4	14	
Vascular risk factors			
Hypertension	7	36	0.02
Dyslipidemia	13	24	0.11
Diabetes mellitus	10	20	0.21
Old stroke	2	6	0.62
Migraine	1	0	0.27
Alcohol	2	0	0.05
Smoking	6	12	0.35
Cardiovascular diseases	4	5	0.34
Sickle cell disease	0	4	0.27
Stroke subtypes according to TOAST classification			
Lacunar stroke	7	19	0.60
Large artery atherosclerosis	3	11	0.74
Cardioembolic stroke	5	12	0.77
Other determined causes	5	10	0.51
Undetermined causes	3	10	0.55
Incomplete evaluation	0	1	0.55
Multiple etiologies	3	9	0.49

derstood. It could partly be because of differences in the risk factor profile in different parts of the world, as well as a result of sociocultural bias in these societies: in other words, it could indicate that males are more likely than females to seek treatment at referral centers, as also speculated by Dash et al. (2014).

The major risk factors in our study were hypertension (50.6%) followed by dyslipidemia and DM, which is similar to the findings of the study performed by Dash et al. in northern India (Dash et al., 2014). The study from Abha (Babtain et al., 2014) also reported hypertension as the commonest risk factor (52.5%) for ischemic stroke in young patients, although the other major risk factors recorded in that study were carotid artery stenosis followed by diabetes (present in 51% and 40% respectively). There have emerged considerable variations between studies with regard to the likely etiologies of ischemic stroke in young patients. In our analysis, lacunar infarction secondary to small vessel occlusion (SVO) was the

commonest cause (30.6%), which is in line with the findings of Babtain et al., (2014). In their study, the highest number of patients showed SVO, but in that study, cardioembolism and undetermined causes also contributed to a similar extent; instead, in a study conducted in Pakistan (Sher et al., 2013), small vessel disease was the least likely etiology to be found in this age group and this trend was even more significant in relatively younger patients: in a subgroup analysis, none of the patients under 29 years of age had stroke secondary to SVO, although this risk increased with increasing age. In the aforementioned comparison between Malaysia and Australia (Tan et al., 2010), a significant proportion of the patients suffering from LI secondary to SVO were from Malaysia (32.8%) making this the commonest etiology among the young population in that country, while the trend was totally different in the Melbourne hospital, where only 14.8% of the patients had LI, making it the least likely etiology. Again, it could be pointed out that different risk factor profiles in different parts of the world contribute to etiology differences. The second commonest etiology in our patients was cardioembolism, affecting almost 18% of the patients, which is similar to the percentages (15-35% of cases) reported in other studies (Kwon et al., 2000; Varona et al., 2007; Putaala et al., 2009; Kittner et al., 1998; Adams et al., 1995; Rasure et al., 2006). Other determined causes (ODC) in our study accounted for 17% of the cases, which is similar to what was observed by Dash et al. (2014) in their study in northern India. In some studies, the prevalence of ODC has been reported to be relatively low — 8% by Al Rajeeh et al. (1991) in Saudi Arabia —, while Lipska et al. (2007), in their series, reported CE stroke to be most common, followed by LAA, while 11.2% of their pa-

Table III - Common etiologies in other determined causes of stroke.

Etiology	N of cases (%)
Sickle cell disease	5 (33.3%)
Arterial dissection	3 (20%)
Protein S deficiency	2 (13.3%)
IV drug abuse	2 (13.3%)
Alcohol abuse	1 (6.6%)
Polycythemia	1 (6.6%)
Amyloidosis	1 (6.6%)

Table IV - Demographic characteristics, risk factors and stroke subtypes according to sex.

Demographics	Males (N=67)	Females (N=18)	p-value
Age	38.66 ± SD 5.5	37.8 ± SD 4.5	0.56
Risk factors for ischemic stroke			
Hypertension	38	5	0.027
Dyslipidemia	32	5	0.10
Diabetes mellitus	29	1	0.002
Old stroke	8	0	0.13
Migraine	1	0	0.78
Alcohol	2	0	0.65
Smoking	18	0	0.007
Cardiovascular diseases	5	5	0.16
Sickle cell disease	1	3	0.02
Stroke subtypes according to TOAST classification			
Lacunar stroke	24	2	0.03
Large artery atherosclerosis	10	4	0.33
Cardioembolic stroke	11	11	0.10
Other determined causes	10	5	0.17
Undetermined etiology	12	1	0.18

tients were classified as stroke of ODC. This difference may be explained or attributed to the availability, in our center, of better diagnostic facilities and newer imaging techniques, which were unavailable in the previous studies, resulting in under reporting of stroke of ODC. Another issue emerging in our study concerns arterial dissection, which is widely considered to be the commonest among the other determined or uncommon causes of stroke in young patients, reported in percentages ranging from 10% to 20% (Schievink, 2001); in our study, on the other hand, it was found in only 3.5% of the total sample (2 patients had aortic, while 1 patient had vertebral artery dissection), while SCD emerged as the commonest other determined etiology (4 patients already had diagnosis of SCD with other complications of SCD at the time of their stroke, while a further 4 were not aware that they were affected, and the diagnosis was made during the work up for young stroke). Two of these 8 patients with SCD were found to have another mechanism underlying their stroke (one had patent foramen ovale and the other had multiple comorbidities accounting for his LI). Sickle cell disease has been attributed as a cause of stroke in around 15-25% of the patients in the literature, and a study done in our hospital in 1991 (Al Rajeh et al., 1991) also showed sickle cell trait to be responsible for a significant percentage, especially in Saudi population. The same study also mentioned an increased prevalence of SCD in KSA and the Middle East. The fact that most of the epidemiological studies have been conducted in western countries where neck massage and other manipulative maneuvers are more common could explain the high percentage of young stroke cases attributed to arterial dissection.

Hereditary thrombophilia (protein S deficiency) was found in 2 (2.3%) of our patients, while IV drug abuse was found in 5.8%; however, the stroke was considered to be secondary to IV drug abuse in only 2 patients, which is in contrast with findings in the western world.

The etiology could not be determined in 15% of the patients seen at our center, which is a much smaller proportion than reported in other studies — studies in Taiwan and in India, as well as other studies have reported the incidence of undetermined etiologies to be 24-36% (Cerrato et al., 2004; Lee et al., 2002; Varona et al., 2007; Dash et al., 2014; Rasura et al., 2006; You et al., 1997; Nedeltchev et al., 2005) —, however it remains in line with the findings of the study done in this same hospital (Al Rajeh et al., 1991), where infarctions with an unknown etiology accounted for 13% of cases. In another study conducted in Saudi Arabia (Awada, 1994), undetermined causes accounted, overall, for 34.5% of a young population of stroke cases, but that study included all types of stroke, and when considering the ischemic stroke subgroup, the cause of cerebral infarction of undetermined origin was 16%, which is similar to our study. This low prevalence of undetermined etiologies in our study compared with other studies in the literature could be explained by the more extensive investigations done in our center, where most of the patients were investigated thoroughly unless a definite cause was either already present or their stroke mechanism could be explained on the basis of the preliminary investigations, as outlined in the methods. Babbain et al. (2014), comparing age groups, reported hypertension, carotid artery stenosis and hyperlipidemia to be significantly

commoner in patients older than 30 years ($p < 0.05$), while other identified risk factors were more commonly noted in patients aged 30 years and younger. Similarly, strokes of unknown etiology were also more prevalent in patients who were younger than 30 years of age. While the findings reported by Dash et al. (2014) in their study conducted in northern India showed opposing findings, as small vessel disease in their study was commoner in younger age group while the CE caused more strokes in the 36-45 age group that represents the geographical variation in risk factor profile that is reflected in stroke subtype as well.

There are several limitations in our study, the first being its retrospective design, and as the patients were recruited over a long period of time, differences in the work-up strategy with regard to advanced imaging and other diagnostic technologies may have been introduced. Another limitation was that it is a hospital-based study and therefore its results may not be generalizable to the general population. Another limitation is the small sample size. However, despite these limitations, the current study provides an insight into the etiologies of and risk factors for ischemic stroke in young adults in Saudi Arabia. Our study highlights the need for aggressive management of traditional risk factors in young adults and also the need for extensive work-up in every patient in order to find correct etiologies.

In conclusion, our results are mostly in accordance with the available literature, with few differences. But as stroke epidemiology is rapidly changing and stroke burden is increasing globally, there is clearly a need for more prompt diagnosis in the emergency setting, and for the development of more efficient methods for early management and intervention. Because the younger population is the backbone of any society and devastating conditions like stroke in this subgroup can particularly be a major burden with a significant economic and social impact. There is also urgent need to increase awareness, among the general public as well among physicians, of the importance of identifying stroke risk factors and etiological causes and of the need to take drastic measures to control modifiable risk factors and prevent stroke-related disability and dependence.

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