

STROKE IN YOUNG ADULTS: A RETROSPECTIVE STUDY OF 68 CASES

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Abstract- Numerous etiologies are responsible for cases of stroke in young adults. This study reviews the causes of two types of stroke (ischemic and intracerebral hemorrhage) in young adults aged 15 to 40 years, admitted to our center (a tertiary care center) from 1997 to 2002. The purpose of this study is to determine the relative frequency of causes of stroke in young adults and compare this with published data in the literature. Using the codes 46.0 to 46.8 of the International Classification of Diseases- 10th Edition (ICD-10), cases were identified from the records of the stroke patients admitted in Imam Khomeini Hospital and the data were collected from their files using a comprehensive questionnaire. Forty-two cases of ischemic stroke (62%) and 26 cases of intracerebral hemorrhage (38%) were identified. The leading cause of ischemic stroke was cardioembolism (38.1%), followed by atherosclerosis in 5 cases (11.9%). Among cardiac causes infarction was attributable to consequences of rheumatic heart disease in 8 cases. In 3 cases a cessation or decrease in dose of warfarin was followed directly by an ischemic stroke. The most leading cause of intracerebral hemorrhage was hypertension (30.8%). Other causes were anticoagulant therapy, intratumoral hemorrhage, aplastic anemia, leukemia, arteriovenous malformations, and chronic active hepatitis. In conclusion, cardioembolism and hypertension were the most leading causes of ischemic and hemorrhagic stroke in young adults admitted in our hospital.

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Key words: Stroke, cerebral infarction, intracerebral hemorrhage, young adults, etiology, epidemiology

INTRODUCTION

The three causes of ischemic stroke are responsible for about 95 percent of cases in all age groups, *i.e.* large vessel atherosclerosis, cardioembolism, and intracranial small vessel disease, constitute only about 50 percent of causes of ischemic stroke in young adults (1-6).

Numerous rare etiologies account for the other 50 percent of cases (1-6). Usually fewer than 5 percent of cerebral infarctions have been reported to occur in young adults (1, 3, 4), although more than 10% has also been reported (5). The reported incidence of ischemic stroke in adults aged 15 to 40 years varies from 6 cases per 100000 in whites in Baltimore (7) to 40 cases per 100000 in Benghazi, Libya (8).

Numerous series of ischemic strokes in young adults have been published (with the lower age limit of 15 to 18 years, and upper age limit of anything between 30 to 50 years). The findings differ markedly between these studies. This is mainly due to differences in investigational intensity, diagnostic

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criteria, and the existence of referral bias in third-level hospitals. The causes and the proportion with 'no obvious cause' depend on these factors, and all these can change as the years go by and as more causes are discovered (9). Advances in technology, including transesophageal echocardiography (TEE), contrast echocardiography, magnetic resonance angiography, duplex ultrasonography, and new biochemical assays, have led to identification of a higher proportion of causes that remained obscure in the past (1, 2). Arterial dissection, which was reported in less than 10 percent of cases in the past (4, 5) is now diagnosed in up to 20 percent of cases (3, 10). Cases of vertebrobasilar dissection, which was rarely diagnosed in the past, are now emerging as a common cause of stroke in young adults (1). Similarly, the use of advanced cardiac imaging has led recently to the identification of more cases of patent foramen ovale (PFO) which is now considered the leading cause of cardioembolism in young adults in developed countries (1-3). Intracerebral hemorrhage (ICH) has been poorly studied in young adults. Only two studies were specifically devoted to this condition (11, 12). However, the causes and their relative proportion are clearly different in this age group. Amyloid angiopathy, which is estimated to cause about 10 percent of all intracerebral hemorrhages, is extremely rare in young adults. In one report, arteriovenous malformation was twice as common as hypertension as the cause of ICH in young adults (11). The objective of the present study was to review the causes of two types of stroke (ischemic and intracerebral hemorrhage) in the young adults admitted to our tertiary care center.

MATERIALS AND METHODS

Using the codes 46.0 to 46.8 of the International Classification of Diseases- 10th Edition (ICD-10), cases were identified from the records of the stroke patients admitted to our center. Records from the years 1997 to 2002 were examined for ischemic stroke and intracerebral hemorrhage, and cases in the age range of 15 to 40 years were identified. The data were collected from the files of the patients using a

comprehensive questionnaire. The main variables were the type and the cause of the stroke. Hemorrhagic infarcts were included in ischemic stroke group. There was no stroke due to small vessels disease in our cases. Other variables are included in table 1. Exclusion criteria were: 1) traumatic cases of intracerebral hemorrhage, 2) the existence of unresolved differential diagnosis and uncertainty about the diagnosis of stroke.3) incomplete investigations about the cause of stroke (Table 1). The data were analyzed by the SPSS software version 9.00.

RESULTS

Sixty-eight cases (4.5%) of stroke in young adults were identified out of 1462 cases in all age groups, Forty-two (62%) of which were ischemic stroke and 26 remainders (38%) were intracerebral hemorrhage (ICH). The female percentage for ischemic stroke and ICH were 52.4% and 53.8% respectively. The distribution of cases by age and sex is represented in table 2. The percentage of cases in the age group of 36 to 40 years was 35.7% in ischemic stroke and 30.8% in ICH. As well 38.4% of cases of ICH were in the age range of 15 to 25 years.

Table 1. Main variables in our questionnaire

A) Necessary for inclusion of patient

Age and sex
Type of stroke (infarction vs. hemorrhage)
Pregnancy or postpartum state
Family history of stroke
History of risk factors (diabetes mellitus, hypertension, hyperlipidemia, smoking, and oral contraceptive consumption)
Results of routine labs
Protein C, S, and antithrombin III
Screening labs for collagen vascular diseases
Physical examination or screening paraclinics for malignancies (including chest X-ray and abdominal sonography)
Echocardiography and carotid Doppler sonography (for ischemic cases)

B) Variables that have been done in some patients in that period of time

Activated protein C resistance (which has been done for 6 patients)
Transesophageal echocardiography and four vessels angiography (each one in 3 patients)

Table 2. Distribution of cases by age and sex

| Age (year) | Male | | Female | | Total | | | | Female in age group | |
|------------|--------|-----|--------|-----|--------|-----|---------|-------|---------------------|-------|
| | Number | | Number | | Number | | Percent | | Percent | |
| | Inf | Hem | Inf | Hem | Inf | Hem | Inf | Hem | Inf | Hem |
| 15-20 | 1 | 3 | 1 | 2 | 2 | 5 | 4.8% | 19.2% | 50% | 40% |
| 21-25 | 2 | 2 | 2 | 3 | 4 | 5 | 9.5% | 19.2% | 50% | 60% |
| 26-30 | 5 | 1 | 4 | 3 | 9 | 4 | 21.4% | 15.4% | 44.4% | 75% |
| 31-35 | 5 | 2 | 7 | 2 | 12 | 4 | 28.6% | 15.4% | 58.3% | 50% |
| 35-40 | 7 | 4 | 8 | 4 | 15 | 8 | 35.7% | 30.8% | 53.3% | 50% |
| Total | 20 | 12 | 22 | 14 | 42 | 26 | 100% | 100% | 52.3% | 50.3% |

Abbreviations: Inf, infarction; Hem, hemorrhage.

Cardioembolism was the cause of ischemic stroke in 16 cases (38.1%). Atherosclerosis was the probable cause of ischemic stroke in 5 cases. The diagnosis of atherosclerosis was based on evidence of atherosclerosis in Doppler ultrasonography of carotid in one case, and the presence of risk factors (long term diabetes, hypertension, smoking and hyperlipidemia) and lack of other causes in four cases. Other causes of ischemic stroke were antithrombin III deficiency, vasospasm due to subarachnoid hemorrhage, and malignancy (endometrial myosarcoma with pulmonary metastasis). Two cases of stroke occurred after arterial catheterization, one for carotid angiography and one for dialysis through subclavian artery. Possible causes of ischemic stroke were oral contraceptive pills (OCP) and mitral valve prolapse (MVP), both in 3 cases. There was not any other risk factor or etiology in these 6 patients. In 10 (23.8%) of cases no cause was identified. The causes of stroke are listed in table 3

History of smoking, hypertension, hyperlipidemia, and diabetes were present in 10, 5, 5, and 2 of the cases of ischemic stroke, respectively. Besides, history of OCP consumption was present in 4 of women with ischemic stroke, but there was a definite other cause for their infarction in some of the patients with these history. Although in one case stroke occurred in the 36th week of pregnancy, and in another in third week of postpartum, these hormonal situations did not include causes of stroke because the former had atrial fibrillation and the latter had infective endocarditis as well. A family history of stroke was present in one case.

Causes of cardioembolism in cases of ischemic stroke are shown in table 4. The underlying disease in cases of prosthetic heart valve and in the case of stroke after cardiac surgery (mitral valve replacement) was rheumatic heart disease (RHD) based on the history. Atrial fibrillation was present in 3 cases of RHD with mitral stenosis (MS). In 3 cases (two with prosthetic valve and one with MS and atrial fibrillation) stroke occurred a few days after the cessation or decrease in dose of anticoagulant therapy with warfarin.

Table 3. Causes of stroke.

| Causes | Number |
|----------------------------|------------|
| Infarction | |
| Cardioembolism | 16 (38.1%) |
| Atherosclerosis | 5 |
| Hypercoagulable state | 2 |
| Vasospasm | 1 |
| Arterial embolization | 2 |
| Oral contraceptive pill | 3 |
| Mitral valve prolapse | 3 |
| No definite cause | 10 (23.8%) |
| Total | 42 |
| Hemorrhage | |
| Hypertension | 8 (30.8%) |
| Anticoagulation therapy | 3 |
| Hemorrhage in tumor | 2 |
| Aplastic anemia | 2 |
| Leukemia | 2 |
| Arteriovenous malformation | 1 |
| Chronic active hepatitis | 1 |
| No definite cause | 7 (26.9%) |
| Total | 26 |

Table 4. Causes of cardioembolism in cases of ischemic stroke

| Causes | Number |
|-------------------------|---------|
| Rheumatic heart disease | 8 (50%) |
| Prosthetic valve | 3 |
| Infective endocarditis | 1 |
| Complete heart block | 1 |
| Atrial septal defect | 1 |
| Coarctation of aorta | 1 |
| Cardiac surgery | 1 |
| Total | 16 |

The reasons were reduction the dose of warfarin for dental procedures, cessation for catheterization, and cessation by the patient. Cases of MVP were not included in definite causes of cardioembolism in table 4.

Cardioembolism was a more frequent cause of ischemic stroke in women than in men (45.5% in women vs. 30% in men). Also, cardioembolism was a more frequent cause of ischemic stroke in the 15-30 year age group than in 31-40 year age group (53.3% vs. 29.6%). Hypertension was diagnosed as the cause of ICH in 8 (30.8%) of cases. Other causes were coagulopathy due to anticoagulant therapy, intratumoral hemorrhage, aplastic anemia, leukemia, arteriovenous malformation, and coagulopathy due to chronic active hepatitis (table 3). In patients with aplastic anemia and leukemia the platelet count was less than 20000.

The pathologies in the cases of intratumoral hemorrhage were ethmoidal chondro-sarcoma, and metastatic synovial sarcoma. The cause of ICH was not detected in 7 (26.9%) of cases. Hypertension was more frequent in the 31-40 year age group than in the 15-30 year age group (50% vs. 14.3%). Hypertension was also a more frequent cause of ICH in women compared with men (50% vs. 8.6%).

DISCUSSION

The proportion of cases with ICH in young adults varies between 9 to 23 percent in different reports (10, 13, 14), although there is a report in which the proportion of hemorrhage was superior to that of infarct (15). In our study the proportion of ICH was

36 percent which is higher than most of the previous studies. Sex ratio usually shows a slight male preponderance in the ischemic stroke in young adults (55-71% males) (1-3, 16), however, in this study there was a slight female preponderance (52.4%). Like other studies the proportion of cases increased with age (1, 2, 5, 7, 17). This increase has been attributed to increase in arterial dissection and cardioembolic cases in Sweden (1), however, in this study, cardioembolic causes actually decreased in the older age groups. Cardiac or transcatheter embolism has been reported to cause 8-35% of ischemic stroke in the developed countries (1-6, 10, 13). In our study, cardiac causes were identified in 38.1% of cases. This higher frequency may be attributed to higher prevalence of rheumatic heart disease in the population referred to our hospital compared to developed countries. In our study, rheumatic heart disease was the leading cardiac cause of ischemic stroke. However, in studies from developed countries paradoxical embolism is now diagnosed as the leading cardiac cause of ischemic stroke in young adults (1-3, 18). Different criteria for diagnosis of atherosclerosis have been used. In some studies diagnosis is based upon the existence of risk factors, while in others evidence of atherosclerotic disease with imaging techniques is required for diagnosis. This may be one of the reasons why there is such a wide range of atherosclerosis being reported as the cause of ischemic stroke in young adults, with as less as 5 percent to as much as 50 percent of cases being attributed to atherosclerosis in different series (4, 5). When stricter criteria are used the rate of atherosclerosis varies between 5 to 23% (1-3, 10, 13). The percent of atherosclerosis in this study was in the lower limit, being 11.4% based on the existence of risk factors. Non-atherosclerotic arteriopathy is another major group of the causes of ischemic stroke. Numerous rare etiologies including inflammatory and noninflammatory diseases, as well as reversible cerebral angiopathies fall into this category. Arterial dissection, including vertebro-basilar dissection, is the most common etiology in this group. In some recent studies it is diagnosed as the cause of ischemic stroke of the young adults in up to 20% of cases (3, 10). In the present study, there were no cases of arterial dissection. A case of

subarachnoid hemorrhage vasospasm was also diagnosed in our study, which is categorized as a reversible cerebral angiopathy.

Hematological disorders have been considered to be the cause of ischemic stroke in 2-16% of cases, most often 5-9% (1-6, 10, 13). However, this was 2.4% in this study.

Stroke associated with MVP was classified as a possible cause of ischemic stroke in 3 patients in this study, because the relation between stroke and MVP is not yet established. The initial findings of Barnett *et al.* in 1976 and 1980 which was obtained using M-mode ultrasonography have recently been questioned. Gilon *et al.* found no evidence of an association between MVP and stroke in young patients in their 10 year prospective study of 213 cases (19). They found MVP in 1.9% of cases of ischemic strokes in patients 45 years old and younger, as compared to 2.7% in control group. Additionally, they found that depending on the direction of the probe the frequency of MVP diagnosed by M-mode ultrasonography can vary between 5% and 55%. Therefore the previous findings showing an association between MVP and ischemic stroke may not be accurate.

Oral contraceptive pills increase the risk of stroke about 3 times (probably less for hemorrhagic stroke). In a large case-control study involving 220 women 16 to 44 years with ischemic stroke and 770 control subjects, the odd ratio for OCP of first, second, and third generations were 4.4, 3.4, and 3.9, respectively (20). OCP has been considered to be the cause of ischemic stroke in 2-5% of cases of young adults (1, 5, 6, 13). However, it is considered a lower priority diagnosis, and a thorough work-up and positive rule out of higher priority diagnosis, i.e. cardiac, atherosclerotic, non-atherosclerotic vasculopathy, and hematological causes is required before OCP can be diagnosed as the cause of stroke (1).

Diagnosis of the cause of stroke in young adults requires extensive evaluation. A thorough search for all higher priority diagnoses should be performed by transesophageal echocardiography, Doppler ultrasonography, carotid-vertebrobasilar angiography, and hematological tests. Only after a complete evaluation the cause can be determined with reasonable certainty (1-6, 10, 13). For instance,

the finding of patent foramen ovale on echocardiography may suggest paradoxical embolism as the cause of stroke. However, angiography may reveal arterial dissection. Since a patent foramen ovale is not uncommon in healthy young adults, priority should be given to arterial dissection in this case (1, 3).

Two studies have been specifically devoted to intracerebral hemorrhage in young adults. In one study, arteriovenous malformations were diagnosed in 20 cases out of 72 patients aged 15 to 45 years (29%). Other etiologies were hypertension (15%), aneurism (9%), and use of sympathomimetic drugs (7%) (11). In another study on 91 patients aged 15 to 40 years, hypertension was the most common etiology, diagnosed in 30% of cases (12). In a study on non-hypertensive cerebral hemorrhages, arteriovenous malformations, tumors, anticoagulant therapy, and amphetamine like agents were emphasized as the main causes in young patients (21). In our study, hypertension was the leading cause whereas arteriovenous malformation was diagnosed in only one case. Coagulopathy associated with anticoagulant therapy was a relatively common cause, found in 11.5% of cases. This emphasizes the need for meticulous control of anticoagulant therapy in patients treated with these agents.

In summary, in this study cardiac causes were the leading cause of ischemic stroke in young adults, and hypertension was the leading cause of intracerebral hemorrhage. Consequences of rheumatic heart disease were responsible for most of the cardiac etiologies. In future, same study with more complete investigations including activated protein C resistance (APCR) and Leiden type of factor 5, G20210A prothrombin mutation, coagulation factor 8 level, homocystinemia and its acquired or genetic causes such as MTHFR mutation, transesophageal echocardiography (TEE), transcranial Doppler (TCD), could be more helpful. Frequency of PFO in patients compared to normal population in our country should be evaluated in a further study.

Conflicts of Interests

We have no conflicts of interest.

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