

Ischemic stroke in young Tunisian adults

Accidents vasculaires cérébraux ischémiques chez les jeunes adultes tunisiens

Dhaker Turki^{1,2}, Salma Sakka¹, Lamia Mbarek¹, Faten Triki³, Mounir Ben Jemaa⁴, Khadija Moalla¹, Sameh Marzouk⁵, Olfa Turki⁶, Fatma Megdiche⁷, Choumous Kallel⁷, Mariem Damak¹, Chokri Mhiri^{1,2}

1. Laboratory of neurogenetics, Parkinson's disease and cerebrovascular disease (LR-12-SP-19), Habib Bourguiba university Hospital, university of Sfax, Tunisia
2. Clinical Investigation Center (CIC), Habib Bourguiba university hospital, Sfax, Tunisia
3. Department of cardiology, Hedi Cheker hospital, Sfax university, Sfax, Tunisia.
4. Department of infectious diseases, Hedi Cheker hospital, Sfax university, Sfax, Tunisia.
5. Hedi Chaker hospital, department of internal medicine, Sfax, Tunisia.
6. Department of intensive care, Habib Bourguiba university hospital, Sfax university, Sfax, Tunisia.
7. Laboratory of hematology, Hbib Bourguiba university hospital Sfax, Tunisia

ABSTRACT

Introduction: Ischemic Stroke in young adults is a real public health problem; it's a major cause of disability, alters quality of life and has a great socio-economic impact.

Aim: determine risk factors and specify the etiology of arterial ischemic stroke in young Tunisian adults.

Methods: In this 5 years retrospective study (2015-2020), we included all young adults (18-50 years) admitted for arterial ischemic stroke (AIS). Risk factors were registered and analyzed. All patients were investigated using a standard protocol: biological tests, brain imaging, carotid ultrasound and cardiac assessment. Additional investigations were carried out at the discretion of the treating physician. The cause of ischemic stroke was classified according to the TOAST criteria.

Results: We collected 200 patients with AIS. The mean age was 41.37 years \pm 6.99. Traditional vascular risk factors were observed in more than 1/4 patients. A definite cause of stroke was identified in 120 patients. Cardio-embolic causes were the most common among our patients (19%) followed by atherosclerosis of the large arteries (11.5%). Other determined etiologies were found in 27.5% of patients. The etiology remained unclear in 40% of cases: undetermined despite complete investigation in 17.5%, undetermined and incompletely investigated 14.5 % and more than one potential pathomechanisms in 8%.

Conclusion: Through this study, we demonstrated the diversity of etiology of stroke in young Tunisian adults. Changes of lifestyle are responsible for the occurrence of the traditional risk factors at an early age. Rheumatic heart diseases remain a frequent cause of AIS in our area.

Key words: Arterial ischemic stroke, young adults, stroke etiology, risk factors prothrombin, G20210A mutation.

RÉSUMÉ

Introduction: L'accident vasculaire cérébral ischémique (AIC) chez les jeunes adultes est un véritable problème de santé publique ; il s'agit d'une cause majeure de handicap, qui altère la qualité de vie et a un impact socio-économique important.

Objectif: déterminer les facteurs de risque et préciser l'étiologie de AIC artériel chez l'adulte jeune tunisien.

Méthodes: A travers cette étude rétrospective sur 5 ans (2015-2020), nous avons inclus tous les jeunes adultes (18-50 ans) admis pour AIC artériel. Les facteurs de risque ont été enregistrés et analysés. Tous les patients ont été examinés selon un protocole standard : tests biologiques, imagerie cérébrale, analyse des vaisseaux du cou et évaluation cardiaque. L'étiologie de l'AIC ischémique a été classée selon les critères TOAST.

Résultats: Nous avons recueilli 200 patients atteints d'AIC. L'âge moyen était de 41,37 ans \pm 6,99. Les facteurs de risque vasculaire traditionnels ont été observés chez plus de ¼ des patients. Une cause précise d'AIC a été identifiée chez 120 patients. Parmi nos patients, les causes cardio-emboliques étaient les plus fréquentes (19 %), suivies par l'athérosclérose des grosses artères (11,5 %). D'autres étiologies déterminées ont été trouvées chez 27,5 % des patients. L'étiologie est restée incertaine dans 40% des cas : indéterminée malgré une investigation complète dans 17,5% des cas, indéterminée et incomplètement investiguée dans 14,5 % et plus qu'une étiologie notée chez 8 % des cas.

Conclusion: A travers cette étude, nous avons démontré la diversité de l'étiologie des accidents vasculaires cérébraux chez les jeunes adultes tunisiens. Les changements de mode de vie sont responsables de la survenue des facteurs de risque traditionnels à un âge précoce. Les cardiopathies rhumatismales restent une cause fréquente d'AIC dans notre région.

Mots clés: AVC ischémique artériel, Jeunes adultes, étiologie de l'AIC, facteurs de risque, Mutation de la prothrombine G20210A.

Correspondance

Salma Sakka

Laboratory of neurogenetics, Parkinson's disease and cerebrovascular disease (LR-12-SP-19), Habib Bourguiba university Hospital, university of Sfax, Tunisia

Email: salma.sakkacharfi@gmail.com

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INTRODUCTION

Stroke is one of the most important causes of disability and is the second most common cause of death worldwide (1). Cerebrovascular ischemic stroke is no more considered as a third age pathology. In fact, multiple studies demonstrated that the incidence of stroke in younger population has increased over the past few decades (2). The proportion of stroke cases occurring in young adults (range 18-50 years) is about 5 to 10% of all cases (3–7) in western countries and increased from 19 to 30% in developing countries (2,8).

A variety of factors are involved in this increasing incidence. The traditional vascular risk factors generally common in elderly such as hypertension, diabetes mellitus, hyperlipidemia plays also a role in the pathogenesis of ischemic stroke in young adults. In addition to later, some factors are more specific for this age range, including altered clotting states, pregnancy (preeclampsia, postpartum, post-abortion...), contraceptive intake, associated to some behavioral practice (smoking, drug abuse, sedentary life style...). Besides the classic etiologies of ischemic stroke, there are a wide variety of rare etiologies specific to this group of patients (4).

Stroke has in general a major consequence on quality of life of the patient but the impact is more important in young adults. It is source of disability, reduction of productivity or loss of employment, drug and rehabilitation expenditure (9). It is therefore essential to determine the exact etiology of stroke to optimize treatment and prevent future vascular events and guarantee better outcomes.

For these raisons, we conducted this study to describe the vascular risk factors and the pathogenesis of ischemic stroke in young Tunisian adults.

METHODS

In this retrospective study, we included all patients aged between 18 and 50 years admitted in our department during a period of 5 years (2015-2020) with either an arterial ischemic stroke (AIS) or a transient ischemic attack (TIA). TIA was defined as a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retina ischemia, without evidence of acute infarction in diffusion-weighted magnetic resonance imaging (10–12). Diagnosis of AIS was established according to the definition of the World Health Organization. The later, considers AIS as condition with a presumed vascular etiology leading to rapid progression of symptoms and loss of neurological function lasting 24 hours or causing death (13). AIS was confirmed by brain imaging (CT-scans or MRI). Patients with cerebral venous thrombosis, sub-arachnoid or intra-cerebral hemorrhage were excluded.

We performed a systematic review of all medical records and collected the pertinent clinical information. For all patients, we specify the baseline characteristics, demographic data and relevant personal and family medical history. We pay also attention for the presence

of any vascular risk factor such as: diabetes mellitus, dyslipidemia, obesity, hypertension smoking, prior stroke or TIA, oral contraceptive use, migraine, coronary heart disease, atrial fibrillation, valvular heart disease and heart failure. All patients were investigated using a standard protocol. Biological assessment included: blood cell count, glucose, cholesterol, electrolytes, transaminases, creatinine, urea, prothrombin time, activated partial thromboplastin time and C-reactive protein. The following additional investigations were carried out at the discretion of the treating physician: Antinuclear antibodies, anti-DNA, lupus anticoagulant, anticardiolipin antibody, antineutrophil cytoplasm antibodies and serologic test for HIV, syphilis, varicella zoster virus and rubella virus. Lumbar puncture was performed in some cases. In addition to cytological and chemical analysis of CSF we searched for tuberculosis and cryptococcosis infections (culture, PCR...). We also carried out genetic tests for coagulation factors such as the G20210A mutation in the factor II (prothrombin) gene and factor V Leiden after giving their informed consent before.

A cardiac assessment was performed including a cardiac trans-thoracic and/or trans-esophageal echocardiography and 24-hour electrocardiography monitoring. We reviewed cerebral imaging for all the patients. We also evaluated the brain supplying arteries by ultrasound and/or CT-angiography.

Stroke subtypes were classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria as (14):

- Large-vessel atherosclerosis
- Small-vessel disease
- Cardio-embolism (due to medium- or high-risk cardiac embolic source)
- Other specific etiology, including non-atherosclerotic vasculopathies (dissection of extracranial arteries, migraine, inflammatory vasculopathy associated with illicit drugs, infections, connective tissue disease ...) and hypercoagulable states.
- Undetermined etiology, which was further classified into three subtypes:
 - Two or more possible causes identified (undetermined, multiple possible etiologies)
 - Negative evaluation after exhaustive etiological diagnostic workup
 - Incomplete evaluation

Statistical Analysis

Statistical analysis was carried out using SPSS 23.0 statistical software. Data on quantitative characterizes are expressed as mean \pm SD and frequencies. Pearson Chi-sq and Fisher Exact tests were used to compare categorical variables across groups, and Student t test to compare means. Probability (p) values of less than 0.05 were considered as statistically significant.

RESULTS

A total of 200 patients (120 males and 80 females) with

a mean age of 40.2 ± 5.7 years were enrolled in this study. They are divided within 2 subgroups: 172 (86%) with AIS and 28 (14%) with TIA. We had an overall male preponderance (male: female ratio 1,5:1). Table 1 summarized vascular risk factors observed in our cohort according to their gender. Mean age at first-ever any ischemic stroke was 41.4 ± 6.7 years. Males were significantly older than females as the mean age was for 42.18 ± 6.44 years for men versus 40.16 ± 7.62 years for women ($p < 0.05$).

The great majority (83%) of our patient had at least one vascular risk factor (one risk factor: 30.5%, two risk factors: 23.5%, 3 risk factors or more: 29%). Only thirty-four patients (17%) had no risk factors. The most common was sedentary lifestyle (49.5%) followed by cigarette smoking (47% of cases) then hypertension, dyslipidemia and diabetes mellitus (respectively 30.5%, 29.5% and 25.5% of cases). Comparison between the two genders shows that obesity, sedentary lifestyle and migraine were significantly more frequent in women however smoking is more frequent in men (Table 1).

Table 1. Vascular risk factors

Risk factor	Men (%)	Women (%)	Total (%)	p
Smoking	75	7.5	47	<0.001
Hypertension	34.2	25	30.5	NS
Diabetes	28.3	21.3	25.5	NS
Dyslipidemia	29.2	30	29.5	NS
Obesity	13.3	38.8	23.5	<0.001
Sedentary life style	41.7	61.3	49.5	<0.01
Migraine	4.2	16.3	9	<0.005
Family history	25	18.6	22.5	NS
Coronaropathy	5	5	5	NS
Cardiac failure	1.7	1.3	1.5	NS
Atrial fibrillation	3	4	3	NS
Valvulopathy	3.3	7.5	5	NS
Malignancy	3.3	5	4	NS
Oral contraceptive	-	13.8	-	-

NS: not significant

A definite cause of stroke was identified in 120 patients (60%). A large-artery atherosclerosis (TOAST 1) was detected in 23 patients (11.5%), almost all of them were over the age of 40 years and the majority were male (respectively 20 and 18 patients). Thirty-eight patients (19%), with a mean age of 40 years, had a cerebrovascular ischemia from a cardiac embolic source (TOAST 2) (Table 2).

Table 2. Etiologies of stroke according to TOAST classification

Etiology	Number	Frequency (%)
1-large vessel disease atherosclerosis	23	11.5
2-Cardio-embolism	38	19
3-Small vessel disease	4	2
4-Other determined etiology	55	27.5
• Thrombophilia	29	14.5
• Cervical arterial dissection	13	6.5
• Cerebral vasculitis	11	5.5
• Fibromuscular dysplasia	2	1
5-Unknown etiology	80	40

The most frequent heart diseases were: atrial fibrillation (21 cases), mitral stenosis (8 cases) and mitral valve replacement (6 cases). Six patients had patent foramen oval associated to auricular septum aneurysm in 3 cases. The other less frequent cardiac diseases were: intracardiac thrombus and recent myocardial infarction (2 cases each), papillary fibroelastoma of mitral leaflet, atrial myxoma, infective endocarditis and akinetic left ventricular segment (one case each) (Table 3).

Table 3. Cardio embolism etiology

Risk degree	Etiology	N	Frequency (%)
High risk	Atrial fibrillation	21	10,5
	Mechanical valve	6	3
	Mitral stenosis	8	4
	Left ventricular thrombus	2	1
	Intra cardiac Tumor	2	1
	Infectious endocarditis	1	0,5
	Recent MI (last month)	1	0,5
	Akinetic left ventricular segment	1	0,5
Low or uncertain risk	PFO	3	1,5
	PFO with ASA	3	1,5
	MI in last 6 months	1	0,5

N: number; PFO: patent foramen oval; MI: myocardial infarction, ASA: aneurysm of inter-auricular septum

Magnetic resonance angiography yielded small vessel disease (TOAST 3) in 4 patients (2%) with a mean age of 48,5.

The other determined etiologies (TOAST 4) were found in 55 patients (27.5%). Among these etiologies, the most common were: thrombophilia (29 cases), cervical artery dissection (13 cases), and cerebral vasculitis (11 cases) with 5 cases of systemic inflammatory vasculitis and 6 cases of infectious vasculitis. Despite complete investigation, the etiology remained undetermined in 35 patients. Sixteen patients had more than one potential pathological mechanisms and the incriminated cause remains uncertain (Table 4).

DISCUSSION

Occurrence of stroke in young adults is a dramatic event that has a considerable socioeconomic impact because of early death, loss of working years and long-term dependency on nursing and social care (15–17). The Helsinki Young Stroke Registry noted relatively low stroke rates during twenties and thirties with sharp increases after the age of 40 (18–20). In this range of age, risk factors and etiology of ischemic stroke are more heterogeneous and differs from elderly in terms of the percent contribution to ischemic stroke. Our study confirmed the diversity of causes of ischemic stroke. In fact, 36 different etiologies were found in our patients. To the best of our knowledge, this study is one of the few and the largest studies that have focused on ischemic stroke in young people in Tunisia (21,22).

In our study, 60% of the patients were males, a percentage quite similar to that reported by most of the studies carried out in eastern countries (23–25) proving that ischemic stroke in young adults is more frequent in men.

Table 4. Etiologies of Stroke of Other Determined Etiology

Etiology	N	Frequency(%)
Dissection of cervical or intracranial artery	13	6,5
Neurofibromatosis	1	0,5
Radiation vasculopathy	3	1,5
Moya-moya	2	1
Fibromuscular dysplasia	2	1
Facteur V Leiden mutation	15	7,5
Antiphospholipid syndrome	11	5,5
Prothrombin gene mutation	2	1
Protein C deficiency	4	2
Protein S deficiency	5	2,5
Antithrombin III deficiency	1	0,5
Leukemia	1	0,5
Vaquez disease	1	0,5
Essential thrombocytosis	1	0,5
Sickle-cell disease	1	0,5
Thrombotic thrombocytopenic purpura	1	0,5
HIV	3	1,5
Cryptococcosis	2	1
VZV	1	0,5
Tuberculosis	1	0,5
Rubella	1	0,5
Takayasu	1	0,5
Wegener	1	0,5
Gougerot-Sjögren syndrome	1	0,5
Behcet disease	1	0,5
Lupus	1	0,5

Less than the third of our patients were under the age of 40, these patients were mostly women. Female predominance in this age range (child bearing age) is explained by the presence of specific risk factors such as oral contraceptive use, pregnancy, migraine and the auto-immune pathologies. At the opposite, after the age of 40 years, most of the patients were men. Indeed, with increasing age, there is an increased prevalence of conventional vascular risk factors such as hypertension, diabetes, dyslipidemia and smoking (26,27). These vascular risk factors were identified in our patients and nearly the half of our patients were smoker. This risk increased with the daily number of cigarettes and number of smoking years. It is reported that up to one-quarter of all strokes are directly attributable to cigarette smoking (28). Hypertension is the most important modifiable risk factor for all types of stroke, it increases by 3 folds the relative of stroke risk (29). In our cohort, 30,5% had high blood pressure without difference between man and women. In the European and American series, the frequency of hypertension exceeded 35% of patients. This difference could be explained by the protective effect of the Mediterranean diet on the blood pressure (30). This diet is also partly responsible of the lower incidence of dyslipidemia in our patients (29,5%) comparatively with in European and American series (respectively 45.8 and 60%)(29, 24). These risk factors generate atherosclerosis leading to AIS type large vessel disease. In fact, patients of our series with large vessel disease had diabetes and consumed tobacco in 70% of cases and had hypertension in 61% of cases. In our series, all the 4 patients with small vessel disease had a high blood pressure. This finding emphasizes the role of hypertension in the pathogenesis

of small vessel disease through several mechanisms, including: hypoperfusion, autoregulatory capacity failure and focal increase in blood-brain barrier permeability (29).

Cardioembolic etiology is a major risk of AIS in young adults, it accounts for approximately one in five strokes (17). It is the most incriminated etiological in our study group (19%). This proportion is concordant with most reported findings (32). Valvular heart diseases were found in 7% of the patients compared to 0,7% in the Finnish study (18). This difference could be explained by the high frequency of rheumatic heart disease in our country (33). Atrial fibrillation (AF) was the most common cardio-embolic cause of stroke in our population (10.5%) of cases. It was presenting 15.1% of patients in the multicenter study of Yesilot et al (34). This value certainly underestimates the actual number of patients with AF. A 3-week telemetry monitoring is recommended for all stroke patients (16). A recent major advance has been developed using insertable cardiac monitors. This strategy is more efficient than conventional strategies for detecting AF (35).

It was demonstrated that more prolonged monitoring allowed to detect dysrhythmia in 23% of the AIS initially classified as cryptogenic (36).

Infectious and systemic causes are less frequently associated with stroke in our series. Infection diseases were incriminated in the occurrence of a vascular accident through local inflammation of the cerebral parenchyma and meninges leading to endothelial dysfunction (7). The human immunodeficiency virus (HIV) was the most incriminated pathogen. Six of our patients were HIV positive (3%) compared to 0.6% observed in the multicenter study reported by Yesilot et al. (34).

Other etiologies were determined including hematologic disorders such as: polycythemia, sickle cell disease, thrombocytopenia, hypercoagulable states especially antiphospholipid antibody syndrome (37). The role of inherited thrombophilia in the occurrence of AIS was largely debated in the literature. Recent studies demonstrated that factor V Leiden, prothrombin G20210A mutation, protein C deficiency, and protein S deficiency are associated with an increased risk of arterial ischemic stroke in young adults (38,39).

In our population, 40% of patients had undetermined etiology. This percentage was slightly higher than what was reported in other series (4,18,40,41). This difference can be partially related to the incomplete diagnostic assessment in some patients. 17.5% of our patients have cryptogenic stroke, no etiology was found despite a comprehensive investigation. The frequency of cryptogenic strokes in the study by Putaala et al was 23% (18), it was 55% in the study by Yesilot et al (34). These cryptogenic AIS remain a challenge and are among the top targets of future stroke research.

Through this study, we demonstrated the large diversity of etiology of AIS in young Tunisian adults. We observed high rates of traditional risk factors at early age due to lifestyle changes. Rheumatic heart diseases remain prevalent and represents a major cause of AIS.

Facing this problem of stroke in young adult, the most important target is to determine the etiology. Diagnostic

approach requires a workup including vascular imaging, testing for hypercoagulable causes, echocardiography... Determination of the exact cause is mandatory to undertake the adequate treatment to prevent recurrence of stroke.

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