ISCHAEMIC STROKE IN THE YOUNG – MANAGEMENT

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Abstract

The incidence of ischaemic stroke in young adults (18-50 years) has increased substantially in the last 3 decades, mainly because of the rising incidence of vascular risk factors in this age group (hypertension, hypercholesterolemia, diabetes mellitus, smoking, obesity) and increased illicit drugs and alcohol consumption. Although progress has been made in early diagnosis of stroke, specific guidelines for the management and secondary prevention of ischaemic stroke in the young are lacking.

Ischaemic stroke in young adults has a considerable socio-economic impact and is responsible for an important decrease in the labor force. While subarachnoid and intracerebral hemorrhage are more frequent in the young population, hemorrhagic stroke still remains less common than ischaemic stroke.

The etiology of ischaemic stroke can be represented by non-atherosclerotic vasculopathy (arterial dissection, inherited or acquired thrombophilia) or cardioembolism in the context of patent foramen ovale and atrial septal aneurysm. In this age group, specific investigations for less common causes of stroke are needed (genetic diseases, autoimmune diseases, vasculitis).

Secondary prevention is of major importance because young patients have a long life expectancy after stroke, including mainly changes in lifestyle, diet and long-term antiplatelet or anticoagulant therapy.

The aim of this presentation is to illustrate recent findings on the heterogeneity of stroke etiology in the young, the adequate case management considering its severe long-term disability and mortality risk and the need for guidelines specifically devoted to ischaemic stroke in this population.

Epidemiology and risk factors

Stroke is the second leading cause of death and third leading cause of disability worldwide [1]. The incidence of ischaemic stroke in young adults (18-50 years) has increased substantially by up to 40% in the last 3 decades, with more than two million young adults having an ischaemic stroke yearly. This rising incidence of cerebrovascular events in this age group can be explained by more advanced neuroimaging techniques (diffusion-weighted MRI), increased incidence of modifiable traditional risk factors and increased illicit and recreational drug use. Women have a higher incidence of stroke considering gender-specific factors such as pregnancy, puerperium, use of oral contraceptives and autoimmune disorders (antiphospholipid syndrome) [2].

Ischaemic stroke in young adults has a considerable socio-economic impact and is responsible for an important decrease in the labor force [3]. Although progress has been made in identifying the etiology of stroke, a large proportion of ischaemic strokes in the young remain cryptogenic. In this age group, specific investigations for less common causes of stroke are needed (non-atherosclerotic arteriopathy, patent foramen ovale, atrial septal aneurysm, genetic diseases) [2].

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Traditional risk factors are also common in the young population, accounting for almost 80% of all ischaemic strokes in this age group, with an absolute increase in the prevalence of hypertension of 4-11%, hypercholesterolemia of 12-21%, diabetes mellitus of 4-7%, smoking of 5-16% and obesity of 4-9% [4]. This rising prevalence is due to a sedentary lifestyle with reduced physical activity, increased salt, sugar, processed food consumption and toxic substances use (smoking, alcohol, illegal drugs) [1]. Obesity is becoming a major health concern worldwide and more children and adolescents are at risk for developing cardiovascular diseases due to the increase of body mass index [5].

TOAST classification of stroke

The TOAST classification of ischaemic stroke can be adjusted according to the most common etiologies in young adults, as seen in Table 1 [2].

1. Large artery atherosclerosis	Atherosclerotic arteriopathy
2. Cardioembolism	Atrial fibrillation and other arrhythmias
	Cardiac tumors
	Cardiomyopathy
	Endocarditis with/without valve vegetations
	PFO or another atrial septum defect
3. Small vessel disease	Genetic cerebral small vessel disease (CADASIL, CARASIL)
	Sporadic cerebral small vessel disease
4. Stroke of other determined cause	Antiphospholipid syndrome, autoimmune diseases, vasculitis
	Cervical artery dissection, intracranial dissection
	Protein C or S deficiency, Factor V Leiden mutation, prothrombin G20210A mutation
	Fabry disease, mitochondrial disorders (MELAS)
	Illicit drug use
	Malignancy, post-radiation
	Reversible cerebral vasoconstriction syndrome
5. Stroke of undetermined cause	Cryptogenic stroke

Table 1. TOAST classification of stroke etiologies in young adults.

Diagnosis and management

The management of young patients with acute stroke is similar to that of the adults. Thrombolysis with intravenous tissue-type plasminogen activator (*IV* tPA) has proven its safety profile and shown more benefits regarding mortality in the young in comparison to the elders. Thrombectomy has shown fewer complications; recent data indicates a high success rate in stent placement in extracranial internal carotid occlusions in young patients with proximal intracranial occlusion performed before thrombectomy. In the case of neurological aggravation due to malignant middle cerebral artery stroke in the first 48 hours, decompressive craniotomy can be considered, as it decreases mortality and improves outcome [2].

Stroke causes and management

1. Cervical artery dissection

Cervical artery dissection is a common cause of stroke in young adults and accounts for 10-25% of strokes in patients under 50 years. Internal carotid artery dissection is more common than vertebral artery dissection. Artery dissections represent separations of the intima from the rest of the vascular wall producing turbulent blood flow, thrombus formation and secondary distal embolism. Possible factors contributing to these vascular lesions are hypertension, migraine, cervical trauma (mechanical forces of rapid acceleration, deceleration and torsional forces), recent intracranial or systemic infection, connective tissue disorders (Marfan syndrome, Ehlers-Danlos syndrome), fibro-

muscular dysplasia, but most artery dissections occur spontaneously and are considered idiopathic [1,2].

The imaging method of choice for diagnosis is cervical and brain axial T1-weighted MRI (fat-suppressed). In the acute stage, intravenous thrombolysis is recommended, except for cervical artery dissections that extend to an aortic dissection [2].

Secondary prophylaxis with antithrombotic therapy is mandatory. Recent studies found no significant difference in recurrent stroke risk or mortality comparing anticoagulation with antiplatelet therapy [6]. The anticoagulation therapy is preferred if the cervical artery dissection causes significant extracranial stenosis or occlusion, or if an intramural thrombus is present, in the absence of an extensive infarction or hemorrhagic transformation. The anticoagulation therapy is contraindicated in case of intradural arterial dissection or with intradural extension, given the increased risk of subarachnoid hemorrhage. If the anticoagulant therapy is initiated, it must be maintained for 3-6 months and then replaced by long-term antiplatelet therapy [7]. Stenting or other endovascular treatment options may be needed for recurrent ischaemic cerebrovascular events despite optimal antithrombotic therapy [8].

2. Illicit drug use

Illicit drug use increases the risk for cerebrovascular disorders, both hemorrhagic and ischaemic stroke, contributing to the morbidity and disability associated with drugs. Studies showed that 12,1% of young adults with stroke had recent drug use and in 4,7% it was considered the only one cause of stroke. Cocaine and amphetamine are most frequently associated with cerebrovascular complications. Cocaine increases the risk of hemorrhagic stroke by 2,33 times and of ischaemic stroke by 2,03 times, whereas amphetamine increases the risk of hemorrhagic stroke by 4,95 times [9]. Even soft drugs previously considered to have no cardiovascular risk, such as cannabis, opioids, ecstasy and LSD, can cause stroke, although less often than cocaine [2].

The effects of the drug depend on drug pharmacodynamics and administration of the drug. A relatively higher proportion of ischaemic strokes has been observed after inhalation compared to other routes of administration (10). Pathological mechanisms modulated by drugs include cerebral vasospasm, cardiac arrhythmias, cardiomyopathy, accelerated atherosclerosis, vasculitis, and direct toxic effects on cerebral vessels. Illicit drug use can be established by history taking, urine, saliva and blood testing [2].

3. Patent foramen ovale

The prevalence of patent foramen ovale (PFO) in the general population is 25%, being responsible for 35-40% of cryptogenic strokes in the young [1,2]. This high proportion highlights the need for PFO screening in young adults with stroke using transthoracic (with contrast) or transesophageal echocardiogram. Major mechanisms involved in the occurrence of stroke are paradoxical embolism, in situ thrombosis at PFO and arrhythmia related to PFO. The risk of stroke in the presence of PFO is higher if it is associated with hypercoagulable states, immobility, pregnancy, or atrial septal aneurysm. Usually PFO related strokes present a lower short-term risk of recurrence compared with those determined by vascular factors [2].

Considering that PFO is relatively common in the healthy population, the RoPE score (Table 2) is used to measure PFO as a causative etiology for ischaemic stroke and guide therapy management [1].

Patient characteristic	**Points**
No history of hypertension	+1
No history of diabetes	+1
No history of stroke or TIA	+1
Nonsmoker	+1
Cortical infarct on imaging	+1
Age	
18-29	+5
30-39	+4
40-49	+3
50-59	+2
60-69	+1
≥70	+0
Total RoPE score	**0-10**

Table 2. The RoPE score.

Secondary prevention for patients with cryptogenic stroke and PFO should consist of anticoagulation therapy, in the presence of deep vein thrombosis or atrial septal aneurysm. In the absence of these factors, antiplatelet therapy is recommended [1]. Recent studies demonstrated that patients with PFO closure have a lower risk of recurrent stroke compared with

those with antiplatelet therapy [11]. However, PFO closure should be performed only in patients with a RoPE score >7, a high degree of interatrial shunt or atrial septum aneurysm [2].

4. Atrial fibrillation

Atrial fibrillation (AF) is the most frequent arrhythmia worldwide. Although AF affects predominantly the elderly with structural heart disease, it can also occur in young adults, older adolescents, and children, being one of the most common causes of cardioembolic stroke in this age group. Strokes due to AF lead to increased mortality and worse functional outcomes. More than 95% of young adults present with symptoms at the onset of AF, such as palpitations and atypical chest pain [12].

Among the leading predisposing factors for AF in the young are obesity, excessive participation in endurance sports, alcohol intoxication ("binge drinking"), thyrotoxicosis and family history of AF. In this population, AF can be determined by a significant rhythm disorder (Brugada, Long QT, Short QT syndromes, paroxysmal supraventricular tachycardia, Wolff-Parkinson-White syndrome) or it can be the first manifestation of a structural heart disease (hypertrophic cardiomyopathy, acute articular rheumatism, congenital heart disease) [12].

The presence of AF in a stroke patient requires anticoagulation therapy for secondary prevention. In case of non-valvular AF, non-vitamin K oral antagonists (NOAC) are indicated, whereas in valvular AF (mechanical artificial valve, mitral stenosis), vitamin K oral antagonists should be used (acenocoumarol), maintaining an INR in the therapeutic range of 2-3. The time of oral anticoagulation initiation is chosen depending on the severity of the ischaemic stroke. The anticoagulation therapy is administered immediately or in the first 24 hours for a transient ischaemic attack, after 3 days for a small sized stroke (<40 mL or NIHSS score <8), after 6 days for a medium sized stroke (40-100 mL or NIHSS score 8-15) or after 12 days for a large stroke (>100 mL or NIHSS score >15) [7].

5. Infectious endocarditis

Infectious endocarditis is a possible cause of ischaemic stroke considered to be cryptogenic in young adults without traditional risk factors, pediatric population, and immunocompromised patients. Cerebrovascular complications in infectious endocarditis are common, with a reported 15-20% in-hospital mortality and up to 40% mortality in the next 1-5 years [13].

Neurologic complications caused by septic embolization in infectious endocarditis consist of large vessel occlusion (more frequently the middle cerebral artery and posterior cerebral artery), smaller scattered emboli in multiple vascular territories, cerebral microhemorrhage and mycotic aneurysms. Left sided infectious endocarditis is associated with increased risk of stroke, especially when involving the anterior mitral valve or if the valvular vegetations measure more than 10 mm. Among the microorganisms isolated in infectious endocarditis with stroke are Staphylococcus aureus, Streptococcus bovis and fungi [13].

Fever and cardiac murmur in a young stroke patient should indicate a possible infectious cause of stroke [14]. Etiological paraclinical investigations in the young include laboratory tests (inflammatory syndrome, leukocytosis, mild anemia), blood cultures and echocardiography.

6. Thrombophilia

As far as thrombophilia is concerned, the genetic profile of the risk includes determination of factor V Leiden, prothrombin, antithrombin III, protein C, protein S, hyperhomocysteinemia, antiphospholipid syndrome, methylenetetrahydrofolate reductase gene mutations. A retrospective cohort study of patients with ages between 18-65 years with acute ischaemic stroke from the Cornell Acute Stroke Registry indicates that at least 40% of patients with cryptogenic stroke have a previously mentioned mutation identified. In terms of clinical case management, only 8% of patients benefited from a change, referring in particular to testing for positive antiphospholipid syndrome [15].

Thrombophilia screening is recommended in young patients with a family history of stroke at a young age or deep vein thrombosis, spontaneous abortions, and autoimmune pathologies. The state of hypercoagulability is a "two hits" phenomenon – caused by both dehydration and inflammation and therefore prolonged immobilization is ought to be avoided regardless [1].

7. Genetic causes

Next-generation sequencing (NGS) studies indicate that deletions in the genes that cause monogenic stroke are very common. In most cases, genetic risk factors contribute to the risk of stroke as part of a multifactorial predisposition, dependent on individual genetic variability; therefore, routine genetic testing has not yet been proven useful. For example, a polymorphism in an intron of the PHACTR1 gene was associated with a modest risk of developing fibromuscular dysplasia and cervical arterial dissection in the first genome wide study (GWAS) involving the respective pathologies [2].

Fabry disease, although rare, is associated with stroke in young adults, but more data is needed to prove a causative connection; therefore, in this case, routine genetic testing is not indicated either [2].

8. Malignancies

Various studies indicate an approximately 40-50% higher incidence of ischaemic stroke among cancer patients (15-39 years), explained by multiple mechanisms: the associated hypercoagulable state, direct tumor effects through vessel compression or tumor embolism, marantic endocarditis, accelerated atherosclerosis and the toxic effects of chemotherapy and radiotherapy. The greatest risk is presented by survivors of CNS, head, and neck tumors and leukemias [1,2,16].

There are no precise indications on screening for malignancies or choice of antithrombotic agent for secondary stroke prevention at young ages in the stroke guideline at the time being [2,16], underlining the necessity to establish a screening program [1].

9. Migraine

There are multiple studies that indicate an increased incidence of stroke in patients with migraine, especially those who present with an aura [2]. The presence of white matter lesions and silent strokes is more frequently seen in migraine patients; however, the clinical significance of the lesions remains unknown [17].

The association between migraine and stroke is due to the increased frequency of hyperlipidemia and hypertension in migraine. Framingham risk score, prevalence of cardiovascular events, family history of cardiovascular events, cholesterol level and blood pressure are more frequently associated in patients with migraine, especially if they also present with an aura [2,17].

The vascular territory tributary to the posterior circulation, with predilection the occipital cortex, is prone to ischaemia because the expansion of the cortical depression starts from the occipital cortex. Vasospasm and hypercoagulable state occur in every migraine attack. The increased prevalence of silent infarcts in the posterior circulation in the case of migraine patients, especially women with migraine with aura, is also proven. Patients with frequent migraines present with isolated cerebral endothelial dysfunction, restricted to the posterior circulation, in the absence of systemic endothelial dysfunction [2].

At the same time, the 5HT1B/1D receptors, which hold an important role in the pathogenesis of migraine, are mainly located in the vertebrobasilar (VB) system and the medication that acts via serotonin receptors is more effective here. Thus, migraine has a role in increasing the incidence of posterior circulation stroke in young patients. Specific medication in migraine includes triptans and ergot derivatives, which have a reversible vasoconstrictor effect, increasing the blood pressure and the risk of developing stroke [2].

There are some conclusions that can be drawn from recent data. Firstly, migraine with aura is more common in young stroke patients. Secondly, migraine with aura is an independent risk factor for stroke in young patients.

10. Pregnancy

Pregnancy and the puerperal period, referring to the last trimester, respectively 6 weeks postpartum, are associated with an increased risk of ischaemic stroke, although the absolute risk of pregnancy-related stroke is thought to be low. Specific pregnancy-related causes include peripartum cardiomyopathy, postpartum cerebral angiopathy (part of the spectrum of reversible cerebral vasoconstrictor syndromes), amniotic fluid embolism, pregnancy hypertension (eclampsia). The most frequent cause remains the state of physiological hypercoagulability found in the last trimester [2].

In terms of diagnosis, native brain MRI with TOF is standard for visualization of arteries; if MRI

is not available or is contraindicated, low-dose brain CT can also be performed [2].

Aspirin (instead of clopidogrel) can be administered during pregnancy and lactation regarding secondary prevention. As far as anticoagulation is concerned, vitamin K antagonists cross the placental barrier and are teratogenic and data available on NOACs is sparse and inconclusive. If anticoagulation is required, low molecular weight heparins are preferred to unfractionated heparin, having a good safety profile and the advantage of not crossing the placental barrier [2].

Currently, future pregnancies in patients with a history of stroke are not contraindicated. Such management of cases should always be discussed in a multidisciplinary team [2].

Long-term sequelae

Ischaemic strokes in the young population have severe long-term medical and psychosocial consequences. Prognosis of stroke in young adults, frequent complications and their risk factors are highlighted in Table 3 [2].

Complication	Prevalence	Risk factors
Post-stroke epilepsy	12%	Severe stroke, stroke caused by large artery atherosclerosis, acute symptomatic seizures (within 7 days of stroke), cortical involvement, territory of middle cerebral artery involvement
Cognitive impairment	>50%	Supratentorial infarction
Fatigue	41%	Depressive symptoms, anxiety, recurrent cerebrovascular events
Depression	17%	Lower educational level, unemployment
Anxiety	23%	Lower educational level, history of depression, unemployment, alcohol consumption
Suicide attempts	>3-6 times more than healthy young people	Male sex, low income, lower educational level, severe stroke (confusion or loss of consciousness), depression
Sexual dysfunction	29%	Depression, ACE inhibitors
Central post-stroke pain	6%	Severe stroke with hemorrhagic transformation
Unemployment	29-33%	Higher NIHSS, female sex, lower occupational status

Table 3. Long-term sequelae and associated risk factors in young adults with stroke.

Conclusions and future research directions

The occurrence of stroke in young adults is one of the causes of mortality and morbidity with a profound impact on disability and physical productivity in young people.

In this respect, prevention remains the most important strategy for long-term clinical and economic outcomes. Risk factors implicated are age, sex, psychological, physical factors, and lifestyle, with the last two regarded as most valuable and needing further studies.

To conclude the aims of this paper, the high mortality, recurrent stroke impact and long-term consequences raise the issue of establishing an even more effective primary and secondary prevention strategy.

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