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Overview

Stroke in young

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Abstract

Stroke is a major healthcare problem ranking as the third leading cause of death and the first cause of disability in the Western countries. Although young adults are at a lower risk of stroke compared to older people, strokes affecting those who are at earlier stages of their productive lives have a greater social impact in terms of number of years of lost productivity and disability. The incidence of stroke in young people ranges between 60 to 200 new cases per year per one million inhabitants, and the overall incidence is about one episode per 100,000 patients per year. Stroke in the young is more frequent in change with industrialized countries, in women, and in blacks and Hispanics compared to whites. In this review we sought to discuss the risk factors, and specific diseases and causes associated with stroke in the young. Moreover, we will discuss the genetic impact on stroke in young, and the outcome and prognosis after stroke among young adults.

1. INTRODUCTION AND EPIDEMIOLOGY

Stroke is a major healthcare problem ranking as the third leading cause of death and the first cause of disability in the Western countries *(1)*. The average age for the incidence of a stroke is >75 years for women, and 71 years for men as reported by American Heart Association in the Heart Disease and Stroke Statistics – 2012 Update *(1)*. Although young adults are at a lower risk of stroke compared to older people, strokes affecting those who are at earlier stages of their productive lives have a greater social impact in terms of number of years of lost productivity and disability. Most of the strokes in the young age are of an ischemic etiology *(1, 2)*. An important issue is the consistent definition of „young" to establish a uniform cut-off to use in various epidemiological studies. Otherwise, comparing the results from different clinical studies in young adults may prove challenging. In fact, apart from a consensus proposal on the etiological investigation of cerebral infarction in young adults from the Societé Française Neurovasculaire *(3)*, no other specific guidelines have been proposed for the management of stroke in this sub-population.

Forty-five years as the upper limit of defining young adults have been used in various studies and appears to be a reasonable boundary. The incidence of stroke in young people ranges from 60 to 200 new cases per year per million inhabitants *(2, 4)*. The overall incidence is about one event per 100,000 patients per year. The incidence is higher in non-industrialised countries *(2, 4)*. A Finland study *(5)* reported a yearly incidence of stroke increasing from 2.4 per 100,000 for people aged 20–24 years, to 4.5 per 100,000 for people aged 30–34 years, and to 32.9 per 100,000 for people aged 45–49 years. Stroke was slightly more

TABLE 1

Risk factors, specific diseases and genetic determinants associated with stroke in young.

Risk Factors in Stroke in Young	Prevalence	References
Hypertension, dyslipidemia, diabetes	45–60%	*18, 19*
Smoking	40–60%	*8, 9*
Migraine	10–35%	*10*
Pregnancy and puerperium	5–10%	*12*
Oral contraceptives	10–22%	*14*
Illicit drugs use	3–12%	*17*
Specific Diseases		
Spontaneous arterial dissection	40–52%	*20*
Fibromuscular dysplasia of carotid and vertebral arteries	10–15%	*20, 25, 26*
Vasculitis and connective tissue disorders Churg-Strauss, Wegener's vasculitis, polyarteritis nodosa, cryoglobulinaemia, Behçet' disease, inflammatory bowel disease, sarcoidosis, systemic lupus erythematosus, antiphospholipid syndrome	6–10%	*27, 28*
Infective diseases syphilis, tuberculous meningitis, acute bacterial meningitis, Varicella-zoster virus, AIDS, hepatitis C, cysticercosis and Chagas disease)	4–8%	*30 – 36*
Hematological diseases paroxysmal nocturnal haemoglobinuria, thrombotic thrombocytopenic purpura, erythrocytosis, leukaemias, and intravascular lymphoma, sickle-cell disease	2–10%	*37, 38*
Cardiac disease patent forame ovale, atrial septal aneurysm, inter-atrial septum, atrial fibrillation, cardiomyopathy, valvular disease and endocarditis	18–30%	*39, 43, 44*
Genetic Determinants		
Monogenic determinants CADASIL, CARASIL, Fabry´s disease, Moyamoya disease	<2%	*45, 46, 52*
Multifactorial Determinants variants in the genes for coagulation factor V, prothrombin, methylenetetrahydrofolate reductase (MTFHR), angiotensin-converting enzyme (ACE), apolipoprotein E (ApoE), rs12425791 SNP	Not Determined	*53 – 57*

frequent in women aged 20–30 years and in men older than 35 years. Also race-ethnicity has been demonstrated to play a role in the incidence of stroke in the young. In the Northern Manhattan Study (NOMAS) cohort, we showed that young blacks and Hispanics have significantly greater stroke incidences than young whites *(6)*.

Incidence, risk factors, and etiology of stroke in young adults differ significantly from those observed among older patients; therefore the knowledge acquired in studies conducted in elderly people with cerebral infarcts is often not applicable to younger people afflicted with stroke. Although, the main clinical challenge in management of a young adult with an acute stroke remains the identification of its cause, our ability to ascertain a specific etiology has improved greatly in the past few decades due to advances in non-invasive imaging technologies that allow a better resolution of the brain vessels, heart anatomical structures and cardiac function.

2. RISK FACTORS FOR STROKE IN YOUNG

Risk factors and etiology for stroke in young adults significantly differ from those observed among older individuals *(9)*. These data are derived mainly from hospital-based case control studies and less often population--based case-control or cohort studies. Traditional vascular stroke risk factors such as hypertension, dyslipidemia and diabetes still have a significant role in younger patients and their role only increases with age. However, risk factors for stroke which are considered *„minor"* in the elderly, have a greater impact on etiology of strokes in the young (Table 1).

Smoking is an important risk factor for cerebral infarction in the young *(8)*. Young adults (15–45yrs old) who smoke are 1.6 times more likely to have a cerebral infarction than a non-smoker (95%CI, 1.07 – 2.42) *(8)*. Moreover, this risk increases with the duration and dose of the exposure, from an odds ratio (OR) of 2.2 (1.5 – 3.3) for one to ten cigarettes per day up to 9.1 (3.2 – 26.0) for 40 or more cigarettes per day *(9)*.

Another important risk factor for stroke in the young is migraine. A recent meta-analysis indicated a significantly higher risk for stroke among people who had a migraine with aura (2.16, 1.53 – 3.03) compared with people who had migraine without aura (1.23, 0.90 – 1.69;

meta-regression for aura status P=0.02) *(10)*. Additional analyses showed how age less than 45 years, smoking, and oral contraceptive use have a synergstic effect on risk. These results were also confirmed in a subgroup from the Women's Health Study after adjustment for major vascular risk factors (age, blood pressure, antihypertensive medication, diabetes, body mass index, smoking, alcohol consumption, menstrual status, hormone levels, oral contraceptive use and cholesterol) *(11)*. A higher incidence of stroke in young adults has been reported during pregnancy and puerperium *(12)*. However, the exactly cause of the stroke in these patients is often not identified. The hypercoagulable state associated with changes in vessel wall function which are typical in pregnancy have been suggested to play a role in the occurrence of stroke *(13)*. Moreover, eclampsia, a typical pregnancy-related disease, has been associated with cerebral vasoconstriction syndrome and with non-haemorrhagic stroke-like episodes *(13)*. The role of oral contraceptives as a risk factor for stroke in young is still not well defined. A meta-analysis conducted on six case-control studies showed no increase in the risk of stroke among women using only progestogen contraceptives (OR=0.96; 95%CI: 0.70 – 1.31) *(14)*. However, the risk for stroke increased fourfold for women who take pills with a high content of estrogen, and is doubled for those who take pills with low estrogen content *(14)*. Another meta-analysis demonstrated that use of oral contraceptive was associated with increased risk of ischemic stroke (RR, 2.75; 95%CI, 2.24–3.38). Smaller estrogen dosages were associated with lower risk (P=0.01 for trend), but risk was still significantly elevated for all dosages. This study concluded that the impact of oral contraceptive may be evaluated as additional 4.1 ischemic strokes per 100,000 non-smoking, normotensive women using low-estrogen OCs, or 1 additional ischemic stroke per year per 24,000 such women *(15)*.

Unfortunately, in the young population stroke is also one of the most common complications of drug abuse. Strokes related to drug abuse may account for up to 12% of all cases in the young *(16)*. Therefore, without a precise diagnosis, screening for illicit drugs should be always done in young patients presenting with stroke. Illicit drugs increase stroke risk regardless of the administration routes. Intravenously used drugs may induce embolisation by injection of exogenous and toxic material. Cocaine or amphetamines may induce stroke by vasoconstriction, platelet aggregation and heart arrhythmias *(17)*.

A study conducted on 253 consecutive first-ever ischemic stroke patients less than 45 years old from Athens Young Stroke Registry showed that smoking (59%) and dyslipidemia (41%) were the most frequent vascular risk factors *(18)*. Recently, another study was conducted to evaluate the vascular risk factor differences in 3,944 patients with first-ever ischemic stroke aged 15 to 49 years from 15 cities in 12 European countries from hospital registries or population-based studies on young adults *(19)*. Overall the top 3 most frequent risk factors were current smoking (49%), dyslipidemia (46%), and hypertension (36%). Interesting, southern European patients were younger compared to northern Europeans, and in both sexes, prevalence of family history of vascular risk factors and cardiovascular disease (CVD) positively correlated with age and stroke risk across all regions.

3. SPECIFIC DISEASES AND CARDIAC PATHOLOGY ASSOCIATED WITH STROKE IN YOUNG

A number of pathophysiologic factors and specific disease have been linked to stroke in the young (Table 1). One of the most common causes of stroke in young adults is spontaneous arterial dissection *(20)*. Cervical dissection commonly affects the extracranial internal carotid artery, starting a few centimetres after the common carotid bifurcation or the vertebral artery. Dissections are usually subintimal and their rupture results in a hematoma with consequent arterial stenosis or occlusion. The pathogenesis of arterial dissection is still not clearly defined. Head and neck trauma may predispose to dissection; however the incidence of stroke in young with these traumas is very low. It seems more associated to a concomitance between vascular risk factors such as hypertension, and genetic factors *(20, 21)*. We previously reported a case of an ischemic stroke patient with the presence of intrapetrous right internal carotid artery dissection and essential thrombocythemia, suggesting that a hematological disorder may cause endothelial dysfunction and predispose to vascular damage such as carotid artery dissection *(22)*. The diagnosis of arterial dissection can be easily made with ultrasound, magnetic resonance imaging (MRI), computer tomography (CT), or catheter angiography *(23)*. Usually, the stenotic lesions resolve in about 70% of cases, whereas recanalization of occluded arteries is less frequent *(24)*.

Fibromuscular dysplasia (FMD) of carotid and vertebral arteries is another potential cause of stroke in young adults. FMD is nonatherosclerotic, noninflammatory vascular disease that may result in arterial stenosis, occlusion, aneurysm and/or dissection *(20, 22, 25)*. Fibromuscular dysplasia is present in abput 15% of patients with a spontaneous dissection of the carotid or vertebral artery and most of these patients are at a high risk of stroke *(26)* (Figure 1). However, pathophysiology of FMD is poorly understood and large international FMD registries are currently ongoing in order to investigate natural history, diagnosis, treatment and potential role of genetics in FMD.

Other potential causes of stroke in young include primary vasculitis, inflammatory and connective tissue disorders. Churg-Strauss, Wegener's vasculitis, polyarteritis nodosa, cryoglobulinaemia, Behçet' disease, inflammatory bowel disease, and sarcoidosis, all may increase the risk for stroke in the young *(27)*. However, the most common immunological disorder associated with stroke in young is systemic lupus erythematosus, antiphospholipid syndrome (SLE) *(28)*. SLE can manifest itself in hypertensive small-vessel disease, cardioembolism, and

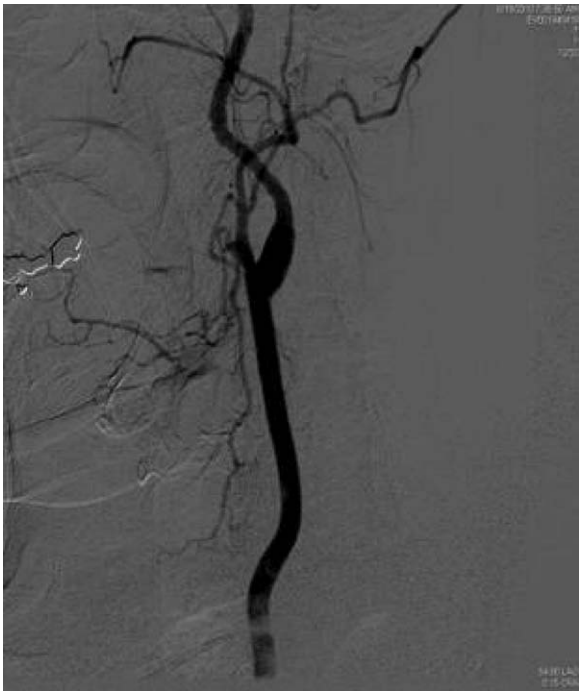

Figure 1. *Fibromuscolar dysplasia of the carotid artery. An anteroposterior view from an angiogram of the left internal carotid artery showing areas of dilation and stenoses consistent with a „string of beads" appearance tipical of FMD.*

the presence of a prothrombotic state as principal risk factors leading to stroke in affected patients *(29)*.

Infectious diseases have also been linked with stroke in the young. Syphilis in its late stage can induce stroke through arteritis of the major brain vessels such as the middle cerebral artery or the deep perforating vessels (Nills-Alzheimer's arteritis), and/or through cardiac complications *(30)*. Cases of stroke have been also reported in young patients affected by tuberculous meningitis *(31)*, acute bacterial meningitis *(32)*, Varicella-zoster virus *(33)*, AIDS *(34)*, cysticercosis *(35)*, and Chagas disease caused by Trypanosoma cruzi *(36)*.

Impacting the coagulation system's ability to increasing or decreasing platelet aggregation and therefore the risk of thrombosis or hemorrhage, hematological diseases such as paroxysmal nocturnal hemoglobinuria, thrombotic thrombocytopenic purpura, erythrocytosis, leukemias, and intravascular lymphoma have been associated with risk of stroke in the young. Among these, the strongest association has been reported for sickle-cell disease (SCD), especially in childhood (*37*). The vessel intima's proliferation with discontinuity of the internal elastic lamina associated with a proliferation of endothelial cells and concomitant thrombus formation has been shown in pathological examination of diseased vasculopathic segments from SCD patients *(38)*.

Cardiac causes account for 20% of all strokes in young; however this percentage is considered a relatively modest proportion compared to their older counterparts. A diagnosis of a cardioembolic stroke is made in patients with brain infarction in a pattern consistent with an embolus in the presence of an appropriate cardiac abnormality, and without another cause for stroke. The risk of embolism is different for different cardiac lesions. Patent forame ovale (PFO) is a common remnant of the fetal anatomy, which is found in 15–25% of the general population. PFO has been identified as an important etiology of stroke in young, especially when combined with atrial septal aneurysm (ASA) *(39)*. A study conducted in a population of 60 adults under 55 years of age with ischemic stroke and a normal cardiac examination demonstrated significantly greater prevalence of PFO in the patients with stroke (40%) than in the control group (10%, $p<0.001$) *(40)*. However, this association was weaker or absent in older patients *(41)*, and the real impact of PFO in stroke is still controversial. For example, in 1,100 stroke-free subjects older than 39 years of age from NOMAS, PFO, evaluated by transthoracic echocardiography, was not significantly associated with ischemic stroke (HR 1.64, 95% CI, 0.87 to 3.09) after adjustment for demographics and risk factors. The same trend was observed in all age, gender, and race-ethnic subgroups *(42)*. ASA is an additional abnormality of the inter-atrial septum (IAS), usually occurring in association with PFO. When present, it tends to occur in association with larger shunts and has been demonstrated to be associated with increased risk of recurrent stroke risk *(43)*.

Minor cardiac pathologies associated with stroke in young include: atrial fibrillation (AF), which is one of the major causes of cardioembolic stroke in elderly. A prevalence of AF is 0.1% among persons younger than 55 years *(44)*. Similarly, other abnormalities of cardiac structure of low prevalence in young adults such as cardiomyopathy, valvular disease, and endocarditis may be causes of stroke in the young *(39)*.

4. GENETIC DETERMINANTS OF STROKE IN YOUNG

Stroke is a heterogeneous multifactorial disorder. Studies conducted in twins, families, and animal models provide evidence for a genetic contribution to stroke, although the real impact of genetics is still unknown *(45)*.

Monogenic Diseases

There are more than 50 single-gene disorders that may cause stroke. However, they account for less than 1% of all stroke cases (Table 1). Monogenic disorders are typically associated with stroke in childhood, with certain stroke types and subtypes, with the absence of other stroke risk factors, and with specific phenotypes of the associated diseases *(45)*. The phenotypic manifestations of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is one of the most common and extensively studied among the monogenic diseases *(46)*. CADASIL is associated with mutations in the *NOTCH3* gene *(46)*. The estimated prevalence of CADASIL in young patients with

stroke is very low (0.5% of lacunar strokes) *(47)*. Low is also the percentage of young developing stroke with cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL) *(48)*. CARASIL is linked to a mutations in the HtrA serine peptidase 1 (*HTRA1*) gene *(49)*.

Fabry's disease is a systemic disorder affecting mainly the kidney, skin, and eye and leading to a painful neuropathy. Fabry's disease is linked to a pathogenic mutations of α-galactosidase enzyme *(50)*. Large-vessel and small-vessel disease are suggestive of Fabry's disease. Studies reported a high frequency of Fabry's disease in the young with cryptogenic stroke *(51)*.

An important role in the development of stroke in the young is played by the Moyamoya disease, a progressive, occlusive, cerebrovascular arteriopathy, characterized by bilateral progressive stenosis of the distal internal carotid arteries or their branches, more commonly involving the circle of Willis, and the development of compensatory collateral vessels *(52)*. The Moyamoya disease is rare in western countries, with an incidence of 0.086 per 100,000 persons per year, while it is more common in African, American or Asian descendants (up to ten-times more common in Japan) *(52)*. The disease has two peaks of age at onset, a juvenile type that occurs at 5 years and an adult type that occurs at 30–50 years. Adults more often suffer of hemorrhagic stroke (subarachnoid, intraparenchymal or intraventricular) caused by the rupture of the collateral vessels that have developed during childhood *(45)*. Loci for the disorder have been mapped to chomosome (ch)3p, and ch8q23. Variations in the (ring finger protein 213) *RNF213* gene on ch17q25 and mutation in the actin, alpha 2, smooth muscle, aorta (*ACTA2)* gene on ch10q23.3 have also been shown to confer susceptibility to the Moyamoya disease *(45)*. However, the clear molecular pathways leading to the Moyamoya disease are still not well-defined.

Multifactorial Polygenic impact in stroke

The genetic contribution to stroke seems to be polygenic and based on many alleles that play a cumulative small effect size. Although limited, candidate gene studies identified several genetic variants associated with stoke in different cohort populations (Table 1), such as common variants in genes for coagulation factor V, prothrombin, methylenetetrahydrofolate reductase (*MTFHR*), and angiotensin-converting enzyme *(53)*. A meta-analysis aimed to determine the genetic risk contributed by each susceptibility gene polymorphism in adult early-onset ischemic stroke patients evaluated twenty-six studies with age ranges 18–50 years for cases with stroke *(54)*. The results showed a significant but modest association just for 2 polymorphisms on *MTHFR* C677T (OR = 1.44, 95% CI = 1.14–1.80) and apolipoprotein E (*ApoE*) epsilon2–4 (OR = 2.53, 95% CI = 1.71–3.73).

Genome-wide linkage studies (GWAS) opened a new era in studing the genetic impact on various diseases. However, although GWAS have the ability to detect single risk loci with relatively large effect, not many GWAS have been conducted in stroke to date, especially in the young. The first GWAS for IS was conducted using more than 400,000 unique SNPs in a cohort of 249 patients with ischemic stroke and 268 neurologically normal controls *(55)*. However, these data did not reveal any single locus conferring a large effect on risk for ischemic stroke. In the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) *(56)*, which consists of four prospective epidemiological cohorts of nearly 19,600 subjects with 1544 incident strokes, two SNPs were identified on ch12, in the region of 12p13, while replication was obtained only for one (rs12425791 SNP; the HR 1.3 fo all stroke, and 1.0 for ischemic stroke). However, only a small subgroup of young stroke patients was included in these studies. The Cervical Artery Dissection and Ischemic Stroke Patients (CADISP) study *(57)* and the Genetics of Early Onset Stroke (GEOS) study *(58)* that focus on unselected young ischemic stroke patients are undergoing and will have the opportunity to address genetic determinants of stroke in the young.

5. OUTCOME AND PROGNOSIS

To date, community based studies have not been very helpful in increasing our knowledge about the outcomes and prognosis of stroke in young adults because of the low incidence of stroke among patients younger than 45. In the Athens Young Stroke Registry, the probability of 10-year survival in young with stroke was 86.3% (95%CI: 79.1–93.6) and the corresponding probability of composite vascular events was 30.4% (95%CI: 19.6–41.2). Stroke severity and heart failure were the main predictors of mortality. At the end of the follow-up period, most patients (93% of survivors) were functionally independent *(18)*. In another study aimed to evaluate the long-term clinical outcome in a large series of young adults (15–45 years) with ischemic stroke the results showed that among the patients enrolled nine (3%) died as the result of their initial stroke; two hundred and ten (88%) were alive with a mean follow-up of 12.3 years and 30 (12%) died during follow-up *(59)*. The average annual mortality rate was 1.4%, and was higher during the first (4.9%) compared with the subsequent years (0.9%) after the initial stroke. Ninety per cent of the followed patients were functionally independent and 53% returned to work. Age over 35 years, male gender, the presence of cardiovascular risk factors and large-artery atherosclerosis in the carotid territory were predictors of negative long-term outcome after the initial stroke. These data suggested that the long-term prognosis for the ischemic stroke in the young is better than in the elderly, but the risk of mortality in young adults with ischemic stroke is much higher than in the general population of the same age *(59)*. A recent study showed that severity and outcome of stroke in children and young adults (up to 40 years) are similar *(60)*.

The Safe Implementation of Thrombolysis in Stroke-International Stroke Thrombolysis Register (SITS-ISTR)

was a clinical trial aimed to assess the safety and efficacy of thrombolysis in 18- to 50-year-old patients with stroke compared to those aged 51 to 80 years *(61)*. A total of 27,671 patients aged 18–80 years treated with IV alteplase within 4.5 hours of symptom onset were enrolled. The main outcome measures were symptomatic intracerebral hemorrhage (SICH), mortality, and functional independence (modified Rankin Scale [mRS]) at 3 months. In the 3,246 (12%) patients aged 18–50, SICH occurred in 0.6% vs 1.9% in those aged 51–80 (OR 0.53; 95% CI 0.31–0.90, p=0.02). Three-month mortality was 4.9% and 14.4%, respectively (OR 0.49; 95% CI 0.40–0.60, p<0.001) and functional independence was 72.1% vs 54.5%, respectively (OR 1.61; 95% CI 1.43–1.80, p<0.0001). These results suggest that thrombolysis is safe in young compared to older stroke patients, and need to be taken in consideration in treatment of this subpopulation of ischemic stroke patients.

6. CONCLUSION AND FUTURE PERSPECTIVES

Stroke in the young is not a rare occurrence. The factors responsible for stroke in young-adults are quite different from those that cause stroke in elderly. Arteriopathy, cardiac diseases, monogenic disorders and multifactorial genetic contributions, in addition to the classical vascular risk factors, represent potential causes of stroke in young. Cryptogenic stroke, where the cause cannot be identified, still accounts for 30% of all ischemic stroke cases in this sub-population. The advances in the imaging technologies and genetic testing may increase the identification of the causes and mechanisms of stroke in young adults. Recent methodologies such as gene expression profiling, proteomics, metabolomics, and the next generation whole genome sequencing technologies aimed at detecting functional changes induced by genetic variations as well as by co-existent non-genetic factor may further help in addressing the causes of stroke in the young. Moreover, multicentre registries and randomized clinical trials specifically dedicated to stroke in the young may help the scientific community to develop efficient guidelines for treatment and prevention of stroke in this important sub-population.

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