



Etiology and diagnostic work-up in young stroke patients

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Abstract

Ischemic stroke is not common in population of the young adults but when they occur, clinical features and evaluation strategies are rather different from adult patients in the usual stroke age group (50 to 85 years). Large epidemiological studies based on hospital-based registries have demonstrated a broad spectrum of aetiologies and risk factors. There is general agreement that young adults have better chances of surviving a stroke than older individuals. However, the majority of survivors have emotional, social, or physical consequences that impair their quality of life. Therefore, it is of great importance to recognize young adults who are at increased risk for stroke and to reduce their risk factors as much as it is possible.

INTRODUCTION

Strokes are not especially common in the young but when they occur, clinical features and evaluation strategies are rather different from adult patients in the usual stroke age group (50 to 85 years).

Cerebral infarction in young adults is responsible for significant socioeconomic loss worldwide. Many studies based on hospital-based registries have demonstrated a broad spectrum of aetiologies and risk factors. In addition, unique aetiologies have also been identified such as Moya-Moya syndrome, vascular dissections, haematological causes, vasculitis and drugs in varying proportions.

Studies on young adults with cerebral infarctions in developed and developing countries have observed large variations in the heterogeneity of stroke subtypes and classification. Interestingly, strokes of undetermined etiology varied widely from 5–44% while combined categories of large vessel atherosclerosis and small vessel occlusion showed similar large variation from 3%–42.5%. The cardioembolic category varied from between 12.6% to 54% among studies while the proportions in the undetermined or unknown category ranged from 15% to 42.5%. Many conventional and recognised risk factors in young stroke patients have also been described. Overall, the results showed these variations due to many reasons including geographical location, referral bias, study methodologies, classification schemes and the intensity of investigations.

There is general agreement that young adults have a better chances of surviving a stroke than older individuals. However, the majority of survivors have emotional, social, or physical disability that impair their quality of life. In addition, young stroke victims are responsible for

providing child care or generating income for their families. Therefore, the ability to predict prognosis would be of paramount importance in this patient population (1–9).

Etiologic variations associated with age

The range of potential etiologies for stroke in young adults is broader than that for older adults. (Table 1)

Like in older adults, stroke in younger adults is typically categorized as primarily ischemic or hemorrhagic. Ischemic etiologies include cardioembolic, atherosclerotic disease, and nonatherosclerotic cerebral vasculopathies. Hemorrhagic strokes include subarachnoid and intraparenchymal types. Of particular note in young adults are stroke causes such as hematologic disorders, substance abuse, trauma, dissections, oral contraceptive use, pregnancy and postpartum states, and migraine.

Cardioembolic Stroke

Cardiac – origin embolism is a very important cause of stroke in young adults. The cardiac disorders responsible are, however, somewhat different than those found in childhood and older adult series. Congenital cardiac disease and atrial fibrillation, congestive heart failure and coronary artery disease-related myocardial dysfunction are not frequent cardiac sources in patients aged 15 to 45. In some recent series, atrial septal defects and patent foramen ovale with or without atrial septal aneurysms are mentioned as the predominant cardiac source of embolism (10).

The potential link between PFO and young stroke remains a controversial subject. Somewhere in the area of twenty-five percent of the population have a PFO, which in itself is not associated with an increased incidence of first ever stroke in large population studies, although a nonsignificant trend toward an association has been observed, particularly among individuals under the age of 60 with an atrial septal aneurysm (ASA). PFO is, however, a more common finding among young patients who present with cryptogenic stroke (11–13).

Thrombophilia in the Setting of PFO and Stroke

While thrombophilia on its own is probably not associated with ischaemic stroke, there is some evidence to suggest that the prothrombin gene mutation, in particular, might confer a greater risk of ischaemic stroke in the setting of a PFO. As nongenetic laboratory assays in the assessment of coagulopathies may be unreliable in the acute phase of stroke, the most reliable studies use genetic testing to identify patients with inherited thrombophilias (14, 15).

Migraine and Stroke

The weight of evidence from case-control studies suggests that migraine, particularly migraine with aura, is associated with an increased risk of ischaemic stroke in

young women under 45 years of age. The pathophysiological mechanism underlying this remains unclear. For one, it is difficult to tease out the relative contribution of cases in which migraine precedes ischaemia (i.e., in which stroke occurs secondary to cerebral hypoperfusion during the aura phase), comprising a migrainous infarct, from cases in which migraine with aura is experienced secondary to ischaemia. True migrainous infarcts are probably rare and tend to affect the posterior circulation. It is also possible that young patients with a history of migraine have an increased incidence of stroke due to a shared underlying etiology which predisposes to both. Migraine as a risk factor for future ischaemic stroke seems to apply mostly to young women, and the relative risk may be as high as 3-fold in those who experience migraine with aura. Several associations which might predispose to stroke in migraineurs have been identified in a small number of case-control studies, including carotid artery dissection and the presence of a patent foramen ovale; however, this does not explain the observed sex difference in the frequency of ischaemic stroke among migraineurs. What is known is that there is an additive risk of stroke in women who experience migraine with aura that smoke, with a greater than 3-fold increase in risk, as well as in those who use the oral contraceptive pill, in whom the risk is quadrupled. An OR of 34 to 35 has been reported for young women who smoke, use the oral contraceptive pill, and experience migraine with aura (16, 17).

Stroke and Puerperium

Stroke complicates an estimated 34 in 100000 deliveries, although reported incidence rates vary from 4 to 210 in 100000 deliveries, contributing to at least 12% of maternal deaths. Some reports suggest that ischaemic and haemorrhagic stroke occur in roughly equal proportions, although ischaemic stroke was more common in one study. This may be due to differences in patient subgroup selection since some studies exclude stroke secondary to cerebral venous thrombosis, which contributes to a significant proportion of ischaemic strokes in the puerperium. Nonetheless, arterial occlusion remains most common. Most strokes occur peri- or postpartum with a relative risk of 8.7 for ischaemia in the first six weeks postpartum, during which cerebral vein thrombosis is also more common, and a relative risk of 5.6 for intracerebral haemorrhage during pregnancy. Looking at intracerebral and subarachnoid haemorrhage combined, a 2.5-fold increased risk of haemorrhagic stroke has been reported in pregnancy, and a 23.8-fold increased risk postpartum. Half of cases of aneurysmal rupture in women under the age of 40 occur in pregnancy. Causes of stroke in pregnancy include haemorrhagic and ischaemic stroke in the setting of pre-eclampsia and eclampsia (25–45% of patients with pregnancy-related stroke), arterial dissection, peripartum cardiomyopathy, paradoxical embolism, amniotic fluid embolism, postpartum cerebral angiopathy, and cerebral vein thrombosis. Cerebral haemorrhage is the most common cause of death in patients with eclampsia but asso-

TABLE 1

Differential diagnosis of ischemic stroke in young adults.

Cardiac disease (including congenital, rheumatic valve disease, mitral valve prolapse, patent foramen ovale, endocarditis, atrial myxoma, arrhythmias, cardiac surgery)
Large vessel disease
Premature atherosclerosis Dissection (spontaneous or traumatic) Inherited metabolic diseases (homocystinuria, Fabry's, pseudoxanthoma elasticum, MELAS syndrome) Fibromuscular dysplasia Infection (bacterial, fungal, tuberculosis, syphilis, Lyme) Vasculitis (collagen vascular diseases — systemic lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome, polyarteritis nodosa; Takayasu's disease, Wegener's syndrome, cryoglobulinemia, sarcoidosis, inflammatory bowel disease, isolated central nervous system angiitis) Moyamoya disease Radiation Toxic (illicit drugs — cocaine, heroin, phencyclidine; therapeutic drugs — L-asparaginase, cytosine arabinoside)
Small vessel disease
Vasculopathy (infectious, noninfectious, microangiopathy) Fabry disease
Hematologic disease
Sickle-cell disease Leukemia Hypercoagulable states (antiphospholipid antibody syndromes, deficiency of antithrombin III or protein S or C, resistance to activated protein C, increased factor VIII) Disseminated intravascular coagulation Thrombocytosis Polycythemia vera Thrombotic thrombocytopenic purpura Venous occlusion (dehydration, parameningeal infection, meningitis, neoplasm, polycythemia, leukemia, inflammatory bowel disease)
Migraine

ciations between pre-eclampsia and eclampsia and ischaemic stroke are also observed. Subarachnoid haemorrhage is the third leading cause of nonobstetric-related maternal death, often secondary to aneurysmal rupture. Whether or not the presence of a patent foramen ovale alone is associated with an increased stroke risk in pregnancy has not been properly examined, nor has the incidence of pregnancy-related stroke in association with peripartum cardiomyopathy. Post-partum angiopathy, a reversible cerebral vasoconstriction syndrome usually occurring in the first week postpartum, may be more common than initially thought, although the exact incidence is unknown. It may or may not be associated with pre-eclampsia or eclampsia and cases have also been seen in association with vasospastic drugs, such as ergonovine and bromocriptine during pregnancy (8–11).

Extracranial Arterial Dissection

Cervical artery dissection (CAD) accounts for up to one fifth of ischaemic strokes in young and middle-aged patients. In a majority of cases, the specific etiology remains unknown. Trauma, infection, migraine, fibromuscular dysplasia, and a range of other causes have been linked with CAD but evidence to support strong links is limited.

With regard to CAD epidemiological observations suggest that some as-yet unrecognized predisposing factors could be heritable. A recent meta-analysis has observ-

ed a probable link with Ehlers-Danlos but no other consistent associations, although there is little doubt that genetic factors play a role given the high proportion of connective tissue defects noted on specimens and the observed clustering of CAD in families. Environmental triggers, such as infection, are likely also important (19–22).

Monogenic diseases

There are more than 50 monogenic diseases that can cause stroke, but they account for a very low percentage of strokes. These disorders are very rare, apart from drepanocytosis, which is an important cause of stroke in children and young adults of African ethnic origin. In young patients of African origin with stroke, sickle-cell disease should always be looked for by use of haemoglobin electrophoresis (haemoglobin S) or genetic testing (Val-Glu substitution in the β globin chain). Follow-up of intracranial stenosis can be done non-invasively with transcranial doppler. Subcortical vascular dementia, depression and other psychiatric disorders, migraine with aura, and recurrent strokes are the main clinical features of CADASIL. The diagnosis is suspected if there is a family history (autosomal dominant) and if MRI shows the characteristic confluent subcortical white matter changes extending to the temporal lobes. The diagnosis is confirmed by skin biopsy and genetic testing (Notch 3 mutations). The estimated prevalence of CADASIL in

young patients with stroke is very low (0–5% of lacunar strokes; 2% in patients younger than 65 years with white matter changes). Hypertension and smoking are associated with an increased probability of stroke in patients with CADASIL, suggesting that vascular risk factors might modulate the clinical expression of this disorder.

The availability of an effective enzyme (α -galactosidase) substitution therapy has led to a renewed interest in Fabry's disease as a cause of stroke in young adults.

Fabry's disease is a systemic disorder affecting mainly the kidney, skin (angiokeratoma), and eye (corneal opacities). It causes a painful neuropathy. The diagnosis in symptomatic men can be confirmed by a deficit in serum α -galactosidase, but usually needs genetic testing, particularly in women, who can have normal concentrations of α -galactosidase.

Vertebrobasilar dolicoectasia and the coexistence of large-vessel and small-vessel disease are suggestive of Fabry's disease. Fabry's disease is more frequent in young patients with cryptogenic ischaemic stroke. In two large multicentre studies of young patients with stroke, α -galactosidase pathogenic mutations were recorded in 2.4% of 493 and 1% of 1000 patients with strokes, more often in those with ischaemic stroke (both cryptogenic and non-cryptogenic). In one of these studies, α -galactosidase pathogenic mutations were more frequent in patients with evidence of small-vessel disease (lacunes or leukoaraiosis; 4.5%), more so if they were not hypertensive (7%), and in normotensive patients with posterior circulation strokes (12.5%). Of importance is the fact that stroke frequently arises before diagnosis of Fabry's disease and in the absence of other clinical findings (23–25).

Cryptogenic stroke

In about 30% of patients, the cause of stroke cannot be identified despite the detailed and comprehensive aetiological work up. Some of these patients might have classic vascular risk factors, but they do not show evidence of large atherosclerotic or small-vessel arterial disease. Minor atherosclerotic lesions might be missed by current diagnostic and imaging techniques. A frequent mistake is the diagnosis of cryptogenic stroke in patients with incomplete or delayed aetiological investigation. This misdiagnosis is of particular importance in dissection, which can resolve quickly, and in intracardiac thrombus, which can either resolve or fragment and embolise. Results of some biological diagnostic tests (eg, antiphospholipid antibodies for antiphospholipid syndrome or platelet count for thrombocythaemia) can fluctuate, and therefore repeated assessment is needed. Repeated or extended Holter monitoring might be necessary if paroxysmal arrhythmias are suspected. Repeated angiography might also be necessary to distinguish between reversible cerebral vasoconstriction syndrome, in which the various segmental arterial narrowings are reversible, and vasculitis, atherosclerosis, or other vasculopathies of intracranial arteries, in which the narrowings persist or even progress.

Diagnostic procedures

The initial work-up should be as expeditious as possible to allow consideration of acute therapies, such as tissue plasminogen activator (t-PA) (26). Brain computed tomography (CT) is usually the initial imaging study of choice as it is readily available and is highly sensitive for acute hemorrhage. Blood work should include a complete blood count with differential and platelet count, prothrombin time (international normalized ratio), activated partial thromboplastin time, glucose, chemistries, electrolytes, serology for syphilis, and an erythrocyte sedimentation rate.

A more detailed coagulation profile (anticardiolipin antibodies, lupus anticoagulants, protein S, protein C, activated protein C resistance, antithrombin III) is requested in patients without a firmly identified cause of stroke or if the patient or family members have a history of thromboses. It is advantageous to send such a profile prior to initiating anticoagulation, as heparin can alter interpretation of some of those assays. Therefore, consider ordering these assays at the beginning of the work-up.

Most patients should have high-quality brain magnetic resonance imaging (MRI) and often MRA (27). Where available, MRI with diffusion-weighted imaging (DWI) and perfusion imaging (PI) is becoming standard. DWI-PI has the potential to distinguish irreversibly injured tissue from that which may be salvageable (28).

Additional studies in initial screening include pregnancy testing, a chest roentgenogram, and an electrocardiogram. An echocardiogram (consider transesophageal), and extracranial (carotid-vertebral) Doppler ultrasound are routinely obtained, although often after initial antiplatelet or anticoagulation therapy is started.

Keep in mind the limitations of studies performed. CT will miss a minority of acute bleeds. MRI with DWI, quite sensitive for acute stroke, has an occasional false negative result (17 out of 782 patients in a recent study). Also, MRA's resolution is not yet on par with conventional angiography.

Consider conventional angiography of cerebral and neck vessels for patients in whom dissection is suspected or in whom no other cause is found. Transcranial Doppler ultrasound can be helpful.

Toxicologic studies are often productive, even when drug use is not acknowledged.

Other blood tests may include homocysteine, fibrinogen, antinuclear antibody, lipid panel, lipoprotein (a), serum protein electrophoresis, hemoglobin electrophoresis, and sickle-cell assay. Cerebrospinal fluid analysis is indicated for cases suspicious for infectious, vasculitic, or occult hemorrhage origins. Telemetry monitoring for arrhythmias is occasionally revealing.

Prothrombin mutation G20210A testing is of uncertain utility in cerebrovascular disease, but may be appropriate for patients with a personal history of thromboembolic disease or family history of thrombophilia (29).

A patient with one or more risk factors, such as migraine or diabetes, should be thoroughly investigated for other possibilities. The cause of stroke in young patients may remain undetermined in 20% to 30% of cases, even after a detailed work-up.

Prognosis. The outcome of stroke in young adults is better than that for older adults. The absence of generalized vascular disease and presence of good collateral circulation often minimizes the eventual brain damage, making the ultimate infarct smaller than in adults. Also, the developing brain shows more plasticity. Undamaged areas can frequently assume the functions of damaged regions. As a result, focal disorders of cognition and aphasia often improve, leaving no major speech deficit, although general intellectual function may be less than expected before the stroke. Although the prognosis is better than in the geriatric age group, strokes in the young are far from benign.

In a recent study of 330 patients with first stroke or transient ischemic attack, followed for an average of 96 months, 8% died, 3% had another stroke, and 3% had a myocardial infarction. Approximately 16% were dependent, but 56% had returned to work. Unfortunately, only a minority of those who smoked at the time of their stroke subsequently stopped using tobacco (30). The overall annual recurrence rate is less than 1%. Prognosis is often closely associated with the underlying cause. A relatively good outcome may be found after many cases of arterial dissection. Risk of stroke recurrence is low (2% over 5 years) in women whose first stroke occurred in pregnancy (31, 32).

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