Chapter

Ischemic Stroke in Young Adults: Practical Diagnosis Guide

Diana Mihai, Florentina Cristina Plesa, Any Docu Axelerad, Alice Munteanu, Minerva Claudia Ghinescu and Carmen Adella Sirbu

Abstract

With its increasing incidence in younger population and as a leading cause of disability, ischemic stroke represents a real public health problem. This chapter aims to evaluate the most common risk factors and causes for ischemic stroke in the young. Though some are identical to those found in older patients, most of them are specific to this population segment. Furthermore, another objective is to provide some guidance in approaching the case based on some important clinical clues. Due to the lack of universal management guidelines, it is up to the physician to judge the particularities of each case and to carry out the variety of investigations necessary for determining the cause.

Keywords: ischemic stroke, young adults, risk factors, etiology, diagnosis guide

1. Introduction

Contrary to the general opinion that it is a disease of the elderly, ischemic stroke is a condition that can occur at any age. Of course, its incidence increases with age, but it has been observed to increasingly affect young people. This tendency can have multiple consequences. Since it targets the young working population, economic and social burden are known to appear.

Although some of the causes or risk factors of ischemic stroke are common for both young and elderly patients, they do not overlap. In young people, the causes can be multiple: heart, vascular, or genetic disorders that require further, sometimes complex investigations. In addition, most cryptogenic strokes appear in this age category. The classic cardiovascular risk factors, which are in present much more prevalent at much younger ages, should also be taken into account.

This chapter aims to illustrate the most frequent causes of ischemic stroke in young people and its associated risk factors and to provide some guidance regarding further investigations necessary for determining the cause.

2. Ischemic stroke in young adults

2.1 Epidemiology

Stroke represents a common cause of morbidity and mortality worldwide. It has been estimated that more than 11 million patients are diagnosed with ischemic

stroke each year [1]. The incidence of stroke varies by geographical area and also by sex, age, and race. Although stroke has been previously considered a disease that is mostly affecting the older population, recent publications show that between 10 and 15% of the total number of strokes occur in younger patients [2]. This means that each year, approximately 2 million adolescents and young adults across the world suffer from an ischemic stroke [3]. Furthermore, recent epidemiological studies have shown that since the 1980s, the incidence of ischemic stroke in the young population has increased, while its incidence in the elderly group has declined. This result raises a few concerns regarding its socioeconomic impact. It occurs in young people with long-life spans ahead, during their most productive years, and causes major long-term disability, with great health-care costs [4]. Some possible explanations for this trend are: improved population awareness regarding stroke symptoms, improved diagnosis performance using advanced neuroimaging techniques, or an increment in the prevalence of the known risk factors (type 2 diabetes, obesity, lack of physical activity, and recreational drug use).

An important question is how is this "young stroke" group defined? Which are its cut-off limits? The majority of authors are using the age of 45 as the group's upper limit [5]. Others favor the age of 49 [2]. This age limit has been arbitrarily drawn based on the major differences in etiologies and risk factors between these two age groups [1].

It has been found that the incidence rate of stroke grows with age, being at its highest in the 45–49 age interval and at its lowest in the group of patients younger than 35 [4].

Incidence rates vary also from a geographical perspective. Developing countries report a higher incidence rate than industrialized ones [1]. Asian countries such as Japan and Taiwan also report higher rates [5]. The "young stroke" incidence is also higher among American blacks and Hispanics. In addition, it has been stated that the hospital stay was longer and mortality higher in black population versus Caucasian [1].

Looking at sex differences, the incidence appears to be higher in men than in women, though some studies have shown that before the age of 30 the incidence of "young stroke" is higher in women [5]. Men have exhibited a higher mortality rate and risk for reoccurring vascular events [1].

2.2 Pathophysiology of ischemic stroke

An ischemic stroke occurs due to a decreased blood flow in a certain area in the brain. This can be the consequences of obstruction of one of the blood vessels that irrigates the brain, or it can occur due to low systemic blood pressure. The most common causes of blood vessel obstruction are thrombosis and embolization. Thrombosis usually develops on atherosclerotic plaques. Atherosclerotic plaques tend to form in larger arteries and are responsible for narrowing the vascular lumen. The process can even lead to the complete occlusion of the blood vessel. The blood clot can embolize distally, causing an ischemic stroke. Though rarely, in situ thrombosis can also occur due to an underlying hematological abnormality (leukemia and polycythemia). Other causes of arterial obstruction are arteritis, arterial dissection, and arteriolosclerosis. Distal embolization is another common mechanism. Most commonly, the source is cardiac. When the source of emboli is in the venous system of the members, the correct term is paradoxical embolization.

When discussing the pathophysiology of ischemic stroke, we most often refer to arterial stroke [6]. Cerebral blood flow (CBF) represents the ratio of cerebral blood volume (CBV) to mean transit time (MTT). There is a directly proportional relationship between CBF reduction and the size of the stroke. Narrowing the vessel

caliber, MTT increases and CBF decreases. To minimize the reduction in blood flow, autoregulation mechanisms start to intervene. Distally to the site of occlusion or stenosis, vasodilation appears, and in addition, the oxygen extraction rate increases. These initial measures help maintain normal perfusion. CBF of 50 ml/100 g brain tissue/min represents the adequate cerebral blood supply. In the ischemic penumbra, FSC is somewhere between 10 and 30 ml/100 g brain tissue/min. The nerve cells in this area can be saved in the first hours after symptoms onset by methods of recanalization of the affected vessel. When FSC drops below 10 ml/100 g of brain tissue, necrosis occurs. The nerve cells in the necrotized area can, at this point, no longer be recovered. ATP depletion, high extracellular K levels, high intracellular Ca levels, cellular acidosis, phospholipases activation, intracellular enzymes, and structural protein alteration eventually lead to cytotoxic edema and cell death. Neural losses are irreversible and begin in the first 4–8 minutes after the onset of ischemia, in the absence of collateral circulation to supplement the cerebral blood flow. In every minute of ischemia, 1.9 million neurons, 14 million synapses, and 12 km of myelin fibers are lost [7].

However, a small fraction of ischemic strokes is caused by venous blood flow abnormalities. Intracranial venous occlusion can cause hemorrhages and compressions and can lead to ischemia [6].

2.3 Risk factors

Conventional cardiovascular risk factors, for instance, hypertension, diabetes, and dyslipidemia, are considered important risk factors for all adults. Their prevalence among the young has been increasing over the last 10 years. Studies show that the most common risk factors found among young stroke patients are: smoking (56%), physical inactivity (48%), hypertension (47%), and dyslipidemia (35%) [2, 4]. On the other hand, among the elderly, the most prevalent ones are hypertension, diabetes, and cardiac diseases such as atrial fibrillation [8]. The tendency toward obesity, the lack of physical activity, the rising number of smokers, and heavy episodic alcohol consumption among teenagers and young adults, which have all been linked to a higher ischemic stroke incidence, are, indeed, worrisome [1].

An interesting observation is that young patients with no vascular risk factors have lower mortality associated with the stroke and fewer recurrences. This means that the number of vascular risk factors can be regarded as an important prognostic factor to determine clinical outcome [8].

Drug use is another important risk factor. It is believed that roughly 5% of the population aged 15–64 use illicit or recreational drugs at least once a year. Such substances associated with ischemic stroke are cocaine, amphetamine, cannabis, and opioids. The negative effects of these substances can be explained either through their direct effects on the cardiovascular system or through complications linked to their administration pathway (embolism or endocarditis related to intravenous administration). The negative effects on cardiovascular system include cardiomyopathies, cardiac arrhythmias, orthostatic hypotension, vasoconstriction, platelet aggregation, accelerated atherosclerosis, and vasculitis. Though previously thought harmless, cannabis consumption can possibly lead to reversible cerebral vasoconstriction syndrome and intimal hyperplasia [3, 8].

Pregnancy and the puerperium are also associated with an elevated risk for ischemic events. Although considered a somewhat scarce occurrence, ischemic strokes associated with pregnancy carry higher mortality rates. The risk is at its highest from the third trimester until 6 weeks postpartum [9]. In countries like India and Mexico, pregnancy-related stroke is not that uncommon and is caused by

dural sinus thrombosis [10]. Causes of ischemic stroke in this category of patients are peripartum cardiomyopathy, hypercoagulability associated with pregnancy, postpartum cerebral angiopathy (reversible cerebral vasoconstriction syndrome), amniotic fluid embolism, or trophoblastic embolism due to choriocarcinoma [9]. Ischemic stroke during pregnancy is also linked to other pregnancy-related complications, as the mechanisms appear to be similar [3]. Special attention should be given to peripartum cerebral venous thrombosis. Risk factors are anemia, first time carrying a pregnancy, and lack of medical care during pregnancy. Frequent signs and symptoms at presentation for patients with this condition are headache, altered consciousness, and motor deficit. Papilledema is observed in up to 80% of patients. Treatment includes anticoagulation, and sometimes, anticonvulsant therapy is also necessary. Prognosis is usually favorable [11].

Contraceptive use raises the risk of ischemic stroke, even more so if associated with smoking or migraines with aura. The risk is tightly linked to the estrogen content in the pill. Progesterone contraceptives do not pose any threat [5, 8].

Migraine with aura appears to be linked to ischemic stroke, especially if tied with other risk factors such as smoking and use of oral estrogen contraceptives. The association is, though, quite controversial [2, 3]. The mechanism is still not known. Its involvement as a risk factor is more evident in young women [5].

Malignancy, along with chemotherapy and radiotherapy, can increase the risk of ischemic stroke, through various mechanisms: direct vessel compression, tumor embolism, nonbacterial thrombotic endocarditis, hypercoagulability, and accelerated atherosclerosis. Current guidelines offer no information regarding cancer screening in young patients presenting for stroke [3].

2.4 Etiology

2.4.1 Cardiac causes

Cardiac embolism is responsible for almost 30% of ischemic strokes in young adults [8]. The most frequent causes of cardiac embolism are presented in **Table 1**.

Although regarded as a frequent risk factor in the elderly, atrial fibrillation is not as prevalent in the young [2]. Due to its paroxysmal occurrence, it is also relatively difficult to diagnose, and it requires continuous monitoring, which is not always justified in younger patients with no cardiac pathology. Other electrocardiographic abnormalities regarding the P-wave have also been associated with higher risk for ischemic stroke [3, 8]. Due to rheumatic heart disease, mitral valve disease should be considered as a potential cause of ischemic stroke in the young. Its prevalence is higher in less industrialized geographic areas [5].

Cardiomyopathies, though rare, should also be considered. Dilated cardiomyopathy is linked to alcohol consumption and occurs at younger age. Chagas disease is more frequent in South America [5]. HIV-associated cardiomyopathy has also been cited as a possible etiology [12]. Peripartum cardiomyopathy is frequent in sub-Saharan Africa. In this case, an echocardiography can help identify the source of emboli [3]. An echocardiography can also identify a cardiac tumor as a source of emboli, such as an atrial myxoma or a papillary fibroelastoma. Atrial myxoma is the most common type of cardiac tumor. It is usually asymptomatic and only discovered after an ischemic stroke. Ischemic stroke can also be a complication of infectious or thrombotic nonbacterial endocarditis. Infectious endocarditis should be suspected particularly if the patient is an intravenous drug user. Thrombosis due to acute myocardial infarction or congestive heart failure is not common causes in young-related ischemic stroke [13]. Patent foramen ovale is a frequent congenital anomaly, found in over 20% of the population. Its prevalence in stroke patients

Cardioembolic cause	
Lower prevalence	**Higher prevalence**
Atrial fibrillation	Congenital cardiac anomalies • Patent foramen ovale • Atrial septal aneurysms
Nonrheumatic valvular disease	Cardiomyopathies
Acute myocardial infarction	Rheumatic valvular disease
Cardiac tumors	Endocarditis

Table 1.
Cardioembolic causes of stroke in the young.

younger than 50 years old is even higher, up to 50%, but its direct role as a causative agent is still debated [8]. Patent foramen ovale is not solely responsible for such consequences, and it also requires other contributing factors such as the simultaneous presence of an atrial septal aneurysm, at rest right to left shunt, larger shunt. Furthermore, additional risk factors for venous thrombosis should be present: prolonged immobilization, long distance travel, varicose veins, trauma, or prothrombotic conditions [4].

To determine whether PFO was the main mechanism in patients with stroke, it is useful to calculate the Risk of Paradoxical Embolism (RoPE) score [14].

The RoPE score (**Table 2**) ranges between 0 and 10 points. A higher score indicates a strong possibility that PFO is the causative agent, while a lower score suggests that PFO could only be an incidental find (**Figure 1**) [4]. RoPE score can also predict the risk of recurrence. A patient with a high RoPE score is a young patient with very few to almost no cardiovascular risk factor and, as a consequence, a very low short-term recurrence risk [3].

2.4.2 Nonatherosclerotic, noninflammatory angiopathies

Cervicocephalic arterial dissection is the origin of ischemic stroke in young patients in 20% of the cases. It affects men in a larger proportion than women (52–69%) [15]. It refers to the intramural hemorrhage of the extracranial arterial segments. The vertebral artery and the internal carotid artery are affected in 90% of the cases [16]. Their cervical extracranial segments are most susceptible to dissection due to their mobility and close proximity to adjacent bone structures such as the transverse processes of the cervical vertebrae. The site of dissection is different than the segment usually affected by the process of atherosclerosis. While atherosclerosis usually develops at the origin of the internal carotid artery, the arterial segments prone to dissection are the distal cervical segments of the internal carotid artery. The vertebral artery, more mobile and prone to injury, is also most affected at its distal extracranial segment, the V3 segment [15, 17].

As a result of a tear in the intimal layer of the vessel, an intramural hematoma will appear. The blood then further extends superiorly along the longitudinal axis of the blood vessel. The hematoma develops between the layers of the media, but if it is situated between the intimal layer and media, the dissection is called subintimal. This type of dissections will most likely narrow the arterial lumen and cause stenosis or even full occlusion of the artery. However, if the blood enters between the tunica media and the adventitia, a dissection aneurysm will occur. This type of dissection is called subadventitial. In this type of dissection, the arterial lumen is not narrowed, and it actually appears widened and can compress adjacent

Patient information	Points
Cortical stroke	1
No hypertension	1
No diabetes	1
No previous stroke or TIA	1
Nonsmoker	1
AGE	
18–29	5
30–39	4
40–49	3
50–59	2
60–69	1
>70	0
Total	

Table 2.
RoPE score [14].

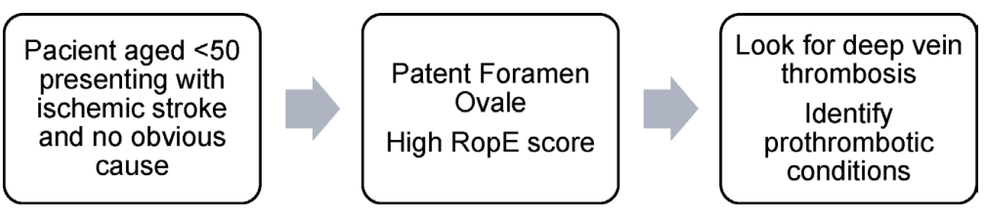

Figure 1.
Pathway to determining etiology of ischemic stroke in patients with PFO.

structures such as sympathetic nerves or the hypoglossal cranial nerve. A blood clot typically forms at the segment of artery affected. The thrombus is not firmly attached to the intimal layer and can easily embolize distally [15, 16, 18]. Dissection of the carotid or vertebral arteries can be accompanied by several signs or symptoms. Headache and neck pain are common. Ipsilateral Claude Bernard Horner Syndrome can occur due to compression of the hematoma on the adjacent sympathetic nerve fibers. Ipsilateral cranial nerve palsies can also be present. These signs can precede the ischemic event with hours or even days in some cases [19].

Predisposing factors to cervicocephalic arterial dissection are: hypertension, recent infection, and migraine. Surprisingly, risk factors for atherosclerosis such as obesity and dyslipidemia are negatively correlated with cervical arteries dissection [19].

A cervicocephalic arterial dissection can appear spontaneously (in 60% of the cases) or after a recent traumatic event [15]. The traumatic events possibly responsible and other risk factors are illustrated in **Table 3**.

Furthermore, arterial dissection can occur on a normally structured blood vessel or on a vessel affected by an underlying arteriopathy (**Table 3**).

An ultrasound examination can suggest the presence of arterial dissections, but the diagnosis is made through angio-magnetic resonance imaging and angio-computer tomography.

Angiography, though an invasive procedure, is the most accurate and precise diagnostic tool.

Underlying nonatherosclerotic, noninflammatory arteriopathies	
Fibromuscular dysplasia	
Moyamoya disease	
Type 4 Ehlers-Danlos syndrome	
Osteogenesis imperfecta type 1	
Pseudoxanthoma elasticum	
Autosomal dominant polycystic kidney disease	
α1-antitrypsin deficiency	
Mechanical trigger factors for cervicocephalic arterial dissection	
Major traumatic events	Cervical spine fracture
	Direct trauma to the anterior neck (punch, strangling)
	Penetrating lesion of the anterior neck
	Sudden and severe rotations of the neck
Minor traumatic events	Sports activities (skiing, tennis, and yoga)
	Forceful coughing
	Vomiting
	Nose blowing
	Sexual activity
	Abnormal, sustained head position
	Prolonged head turning
Iatrogenic cause	Chiropractic manipulation of the neck
	Resuscitation
	Anesthesia

Table 3.
Underlying nonatherosclerotic, noninflammatory arteriopathies and mechanical trigger factors for cervicocephalic arterial dissection.

2.4.3 Inflammatory diseases

The term vasculitis groups a series of diseases characterized by inflammation of blood vessel walls. Inflammation of blood vessels, possibly accompanied by varying degrees of necrosis, can lead to stenosis, vessel occlusion, or aneurysmal dilation. Both arteries and veins can be affected, regardless of their size. Vasculitis that affects the central nervous system can be either primary or secondary to a systemic disorder [19].

Primary angiitis of the central nervous system (PACNS) usually affects small vessels (precapillary arterioles). The lesions are multifocal, which makes it difficult to diagnose. A normal biopsy does not rule out PACNS. It can affect both brain and spinal cord, but no other organs are affected. Its evolution is heterogenic, but it usually presents in a recurrent remitting fashion. Sometimes, it can be rapidly progressive, leading to exitus in a matter of days [20]. The cause of PACNS is not known, but studies show that it is usually associated with other diseases such as Hodgkin lymphoma, leukemia, primary intracerebral lymphoma, HIV infection, and Varicella Zoster virus infection. Most frequently, the clinical picture includes headache and altered cognition, sometimes seizures. Systemic symptoms and signs

such as fever, fatigue, weakness, loss of appetite, and weight loss are very rarely seen. Blood inflammatory markers such as C-reactive protein and erythrocyte sedimentation rate (ESR) are usually normal or slightly elevated. So is blood cell count. The cerebrospinal fluid analysis shows signs of inflammation.

Many systemic vasculitides can affect the central nervous system. Some of the most common are briefly presented in **Table 4**. Other causes of noninfectious angiitis include drug use, radiotherapy, and neoplasia [20].

When the central nervous system is affected, the clinical picture typically includes headaches. Other signs and symptoms that may be suggestive are fever, weight loss, dermatological findings (rash and livedo reticularis), articular lesions, and kidney disease. The inflammation markers such as C-reactive protein and ESR are usually elevated. Other frequent findings in blood tests are anemia, thrombocytopenia, and low complement levels. Cerebrospinal fluid also shows increased level of proteins and inflammatory cells [19].

In a young patient presenting with ischemic stroke with accompanying suggestive symptoms, a systemic angiitis should be suspected. Determining ANCAs and dsDNA antibodies can, in this particular case, be of an important value for determining an underlying condition causing the stroke (**Figure 2**) [21].

2.4.4 Infectious diseases

Some infectious diseases are linked through various mechanisms with ischemic stroke. Some infectious agents tied to secondary vasculitis are presented in **Table 5**. Infections involved in the pathogenesis can be either viral, bacterial, parasitic, or fungal [22].

HIV infections can predispose to stroke through various mechanisms. One pathogenic pathway is large vessel HIV arteriopathy. The arteriopathy may be due to the direct pathogenic effect of the virus. As a consequence of the vasculopathy, large, hemispheric infarctions can appear. Another possible pathogenic pathway is through opportunistic infections of the central nervous system, which can occur as HIV is responsible for an immunosuppressive state. Such opportunistic infections are tuberculosis, Varicella-Zoster virus infection, toxoplasmosis, and syphilis [20].

Tuberculous meningitis is a severe condition with a high mortality rate. Up to 45% of patients diagnosed with tuberculous meningitis develop a stroke, sometimes even multiple strokes [20, 22].

Systemic angiitis affecting the central nervous system	
Large-vessel angiitis	Takayasu's disease
Medium-vessel angiitis	Polyarteritis nodosa
	Kawasaki disease
Small-vessel angiitis ANCA +	Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)
	Granulomatosis with polyangiitis (Wegener granulomatosis)
	Microscopic polyangiitis
Angiitis associated with connective tissue disease	Systemic lupus erythematosus
	Rheumatoid arthritis
	Behçet disease

Table 4.
Systemic angiitis that affects the central nervous system.

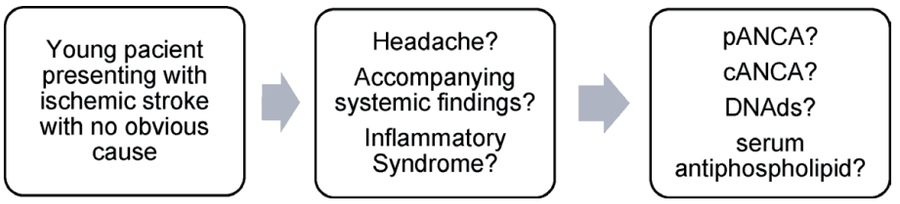

Figure 2.
Pathway to determine etiology in young patients with ischemic stroke.

Infectious agents linked to secondary vasculitis	
Viral infections	HIV (AIDS) Hepatitis B and C Varicella-Zoster virus infection Cytomegalovirus infection
Bacterial infections	Tuberculosis Lyme neuroborreliosis Bacterial meningitis Syphilis Mycoplasma pneumoniae infection Brucellosis
Parasitic infections	Cysticercosis Chagas disease Trypanosoma cruzi infection Leptospirosis Malaria
Fungal infections	Cryptococcus infection Aspergillus infection

Table 5.
Infectious agents linked to secondary vasculitis [2, 20].

Among parasitic infections, Chagas disease and cysticercosis are most commonly involved. Up to 10% of the patients with neurocysticercosis develop strokes (ischemic strokes occur more frequently) [20, 22].

Fungal infections most commonly affect patients who suffer from immunosuppression. Ischemic strokes represent an unfortunate complication. Cryptococcus infections and aspergillosis are linked to HIV infection [20].

In the present context of Covid-19 pandemic, it is important to emphasize the link between the infection and a prothrombotic status. Thrombotic complications represent a frequent find in patients infected. For this reason, the risk of ischemic strokes should also be taken into consideration [23].

2.4.5 Hematological diseases

A large number of hematological diseases predispose to stroke. The mechanisms behind this predisposition are increased blood viscosity, which in return decreases blood flow and hypercoagulability. Even though, a single factor cannot by itself be the only cause for the ischemic stroke, a combination of such predisposing factors can have such unwanted consequences. Some conditions that lead to an increase in blood viscosity are leukemia, intravascular lymphoma, sickle cell anemia, erythrocytosis, polycythemia vera, Waldenström's macroglobulinemia, paraproteinemia, and spherocytosis. Even though coagulopathies are mostly associated with venous thrombosis, recent studies show that deficiency in certain factors involved in blood

clotting such as Protein C, Protein S, antithrombin, and Factor V Leiden mutation increases the risk of arterial thrombosis [19].

Factor V Leiden mutation is a single point mutation that leads to protein C activity resistance. The result is generation of high levels of thrombin, which in turn raises the risk for thromboembolic events. Heterozygosity or homozygosity for this mutation is usually associated with other hereditary coagulation abnormalities [24].

Prothrombin gene mutation is another frequent hereditary disease that interferes with normal blood coagulation. Patients with prothrombin gene mutation have higher than normal levels of prothrombin, which predisposes to thrombosis. This condition is associated with cerebral venous thrombosis, especially when there is a second risk factor involved, like the use of oral contraceptives [24].

Protein C and Protein S are proteins that inhibit the coagulation cascade. Their deficiency predisposes to blood coagulation and can be genetic, or, in some cases, acquired. Conditions associated with Protein C and Protein S deficiency are contraceptives use, pregnancy, severe infections, liver diseases, disseminated intravascular coagulation, and certain medications such as methotrexate and cyclophosphamide [24].

Antithrombin III (ATIII) deficiency is a genetic disease inherited in an autosomal-dominant pattern. Its prevalence in the population is 0.2%. Its role is to inhibit the generation of thrombin. Antithrombin deficiency can also be acquired: severe infections, cirrhosis, disseminated intravascular coagulation, and nephrotic syndrome [24].

None of the conditions described above (Factor V Leiden mutation, prothrombin gene mutation, Protein C and S deficiency, and ATIII deficiency) can cause, by themselves, without additional risk factors, in situ arterial thrombosis. On the other hand, Antiphospholipid Antibody Syndrome is known to cause venous, as well as arterial thrombosis. Ischemic stroke is a recognized complication of this syndrome [24].

2.4.6 Genetic diseases

Family history of stroke at a young age should be suggestive for a genetic cause. Many genetic abnormalities have been linked to the possibility of ischemic stroke. However, stroke represents the main manifestation in only a few genetic diseases.

Periventricular lesions with predominant temporal pole involvement may suggest an autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy CADASIL, with autosomal dominant transmission. Although rare, it is an undiagnosed affliction, so its prevalence may be underestimated. The condition is characterized by a mutation in the NOTCH3 gene located on chromosome 19. The NOTCH3 gene is expressed almost exclusively in smooth muscle fibers and encodes a receptor located at the cell surface. NOTCH3 gene mutation leads to smooth muscle degeneration. The condition starts manifesting between the age of 30 and 60. Patients present with recurrent ischemic strokes, migraine with aura, mood swings, and progressive cognitive impairment. Severe leukoaraiosis is seen on imagining. Temporal lobes are typically involved [19, 25].

Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL) is a much rare disease than CADASIL and affects almost exclusively the Japanese population. It is characterized by a mutation in HTRA1 gene, which encodes HtrA serine peptidase/protease 1 (HTRA1). The clinical picture includes alopecia occurring at young age, low back pain, progressive cognitive impairment, and lacunar strokes [19, 26].

CARASAL is another vascular leukoencephalopathy with R325C mutation in CTSA gene [27].

In other genetic diseases, such as Fabry disease or homocystinuria, though not considered a representative feature, ischemic stroke is strongly linked. Fabry disease has X-linked transmission. It is characterized by a reduced activity of the α-galactosidase enzyme, an enzyme involved in lipid metabolism. As a result, lysosomal lipid accumulation occurs in endothelial cells and smooth muscle fibers of blood vessels. This process can have many unwanted consequences, including ischemic stroke. The diagnosis is made by dosing the enzyme value in patient's blood.

Homocystinuria is a genetic disease transmitted in an autosomal recessive pattern and characterized by high levels of homocysteine in blood and urine. The cause is a deficit in an enzyme called cystathionine β-synthase. The clinical picture includes Marfanoid appearance, mental retardation, premature atherosclerosis, and thrombembolic events.

MELAS (mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes) is caused by mutations in mitochondrial DNA. Ischemic strokes appear before the age of 40. The occipital lobes are typically affected [26].

2.4.7 Venous ischemic stroke in young

Cerebral venous thrombosis (CVT) is a rare affliction, occurring mostly in the younger population. Seventy-five percent of the patients diagnosed with CVT are young women [19]. Even though if mostly affects young women, it can occur at any age, children and newborns also being affected.

Hormones clearly play a role in the pathophysiology of the disease. Its incidence is higher during pregnancy and postpartum (especially in countries such as India and Mexico). It is also correlated with oral contraceptive use and other hormonal therapies [28].

Other risk factors for CVS are hematological diseases that cause blood hypercoagulation and other coagulopathies, infections of the central nervous system, sinus and ear infections or other infections occurring in the region of head and neck, and severe systemic infections (HIV, tuberculosis, and sepsis). Malignancy, systemic inflammatory diseases such as SLE and sarcoidosis and several inflammatory angiopathies are also linked to CVT. Other events linked to CVT are head trauma, brain surgery, and lumbar punctures [29].

The obstruction of dural venous sinuses or intracerebral veins hinders blood drainage and leads to increased pressure above the obstacle. As a result, in the affected area of the brain, edema develops. Arterioles and capillaries can break and hemorrhage appears. In addition, if the tissue pressure becomes higher than the arteriole's pressure of perfusion, ischemia installs [28].

Transverse sinuses and superior sagittal sinuses are most affected. Sometimes, multiple areas in the brain can be affected [19].

The clinical onset is typically gradual, but a sudden onset is also possible. The clinical picture includes headache, seizures, focal neurological signs, and altered consciousness. A useful sign is the presence of papilledema.

Blood tests show elevated D-dimer levels.

Neuroimaging is the most helpful tool in the diagnosis process. A CT scan can visualize parenchymal hemorrhage and tissue edema. Sometimes, the thrombus can be seen on imaging as a hyperdense lesion. MRI is an even more sensitive method, which can better characterize the abnormalities in the brain parenchyma. It can reveal recent infarction, hemorrhage, and tissue edema. These imaging techniques also help identify some predisposing factors such as sinusitis, mastoiditis, cerebral tumors, or abscesses. They are also extremely useful in the differential diagnosis process [28].

CVS is a condition that can now benefit from rapid diagnosis with IRM techniques. When rapidly identified and specific measures applied, the prognosis is favorable, the condition having a low mortality rate [19].

Anticoagulation is the therapy of choice, even if imaging also shows hemorrhage. Thrombolytic therapy has not proved to be superior to anticoagulation. It is used only when anticoagulating agents fail. Sometimes, when the etiology of thrombosis is identified, it may require specific treatment. The patient may require antibacterial or antiviral therapy, antineoplastic agents. In case of severe cases of raised intracranial pressure, decompression techniques may be performed [28].

2.4.8 Cryptogenic stroke

Despite all the diagnostic advances, up to 35% of ischemic strokes, especially in young people, have no identified cause [20].

2.5 Diagnosis

For determining the underlying cause of ischemic stroke in the young, certain clinical clues can be of great value (**Table 6**). Depending on the clinical picture, routine investigations can be then followed by additional, more specific tests (**Table 7**) [19, 20, 30].

Apart from the usual test in young patients presenting with ischemic stroke (complete blood count, blood glucose, hemoglobin a1c, lipid panel, heart enzymes CK, troponin, electrocardiogram, liver and kidney function, ESR, CRP, serum electrolytes, PT, INR, APTT, pregnancy test, urine analysis, brain imaging, and chest X-ray), specific ones will be made depending on the diagnostic suspicion (**Table 7**) [20, 30].

2.6 Differential diagnosis of ischemic stroke

There are many conditions (vascular or nonvascular) that may simulate an acute ischemic stroke. One study reveals that 14% of patients that had presented with acute neurological deficits were falsely diagnosed with ischemic stroke and received thrombolytic medication. The reevaluation proved to be, in fact, a stroke mimic. The differential diagnosis may differ depending on the age of the patient. In general, in a young patient presenting with sudden focal deficit, the following should be taken into consideration: hemorrhagic stroke, cerebral venous thrombosis, complicated migraine, seizures, acute vestibular syndrome, central nervous system tumor or abscess, multiple sclerosis, myasthenia gravis, alcohol intoxication, drug or medication toxicity, hypo or hyperglycemia, dyselectrolytemia, uremia, hyperthyroidism, hepatic encephalopathy, hypertensive encephalopathy, Wernicke encephalopathy, cardiac syncope and psychiatric disorders [10, 31, 32].

2.7 Treatment and prognosis

The clinical presentation, treatment, and clinical outcome depend on the type and cause of stroke. After the etiology of stroke is identified, management and prevention are individualized [2].

The therapy of choice remains intravenous thrombolysis with recombinant tissue plasminogen activator. Young patients tend to have fewer complications, if the therapy is administered faster and the outcome is favorable. Bleeding risk is substantially decreased. The delay between presentation and therapy initiation is usually caused by difficulties in diagnosis [33].

Clinical clue	Suspicion
Fever	Infection Connective tissue disease Vasculitis
Lymphadenopathy	Lymphoma Infection
History of asthma	Churg Strauss syndrome
History of recent head trauma	Arterial dissection In situ arterial thrombosis
Headache	Hereditary endotheliopathy, retinopathy, nephropathy, and stroke (HERNS) Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) Reversible cerebral vasoconstriction syndrome (RCVS) Arterial dissection Vasculitis Systemic lupus erythematosum (SLE)
Acroparesthesia	Fabry disease
Erythema migrans	Lyme disease
Oral/genital ulcers	Syphilis SLE Behçet disease Herpes simplex
Angiokeratomas	Fabry disease
Erythema nodosum	Connective tissue disease Tuberculosis Poststreptococcal infections Sarcoidosis Behçet disease
Butterfly erythema	SLE
Splinter hemorrhages underneath the nail	Endocarditis
Raynaud syndrome	Connective tissue disease Neoplasia Blood hyperviscosity
Needle puncture signs	Drug use
Tattoos	HIV infection Hepatitis
Alopecia	Systemic lupus erythematosus (SLE) Temporal arteritis Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL)
Xanthelasma	Hyperlipidemia
Decreased vision	Mitochondrial disease HERNS Pseudoxanthoma elasticum
Claude Bernard Horner Syndrome	Carotid dissection
Dry eyes	Sjögren syndrome
Iritis	Behçet disease
Roth spots	Endocarditis

Table 6.
Clinical clues in ischemic stroke in the young.

Additional investigations	
Blood/urine toxicology	**Drug use**
Arterial blood gas analysis	MELAS
Rheumatoid factor Complement level dsDNA antibodies ANA antibodies Anti Ro, anti La antibodies Scl 70 antibody Anticentromere antibody Anticardiolipin antibodies Cryoglobulins Serum angiotensin-converting enzyme	Connective tissue disease/other rheumatic diseases
ANCA antibodies Fluorescein angiography	Systemic angiitis
Electrophoresis	Paraproteinemia
Hemoglobin electrophoresis	Sickle cell disease
Specific tests for syphilis, tuberculosis, herpes, HIV, Lyme, and hepatitis	Infectious disease
D-dimers	Thromboembolism
Protein S, Protein C, Factor V Leiden, antithrombin, prothrombin gene mutation	Coagulation abnormalities
Echocardiography	Patent foramen ovale Cardiomyopathy Endocarditis
Holter electrocardiogram	Atrial fibrillation
Lower extremity ultrasonography (in patients with PFO)	Deep vein thrombosis
Coombs test	Hematologic abnormalities
Bone marrow biopsy	Hematologic abnormalities
Cerebrospinal fluid examination (cellularity, glucose, proteins, oligoclonal bands, and infectious agents)	
Arterial/skin/muscle biopsy	Giant cell arteritis CADASIL CARASIL Mitochondrial disease
Brain biopsy	Primary cerebral vasculitides
α-Galactosidase enzyme level	Fabry disease
Homocysteine level	Homocystinuria
Genetic tests	CARASIL/CADASIL and others
Advanced imaging techniques	Personalized, depending on clinical suspicion

Table 7.
Specific additional investigations for young stroke etiology.

Studies show that the mortality in young stroke patients is up to four times higher in the first 20 years after the stroke than healthy people [3]. It has also been observed that cardiac insufficiency and stroke severity are important mortality predictors [2].

Because we are referring to a younger, still employed population, the socioeconomic burden cannot be neglected. We learn from studies that up to one third of patients who suffered an ischemic stroke remain unemployed even up to 8 years after the episode. This may be due to the disability or solely the consequence of depression. Depression following the stroke is a frequent find between this segment of patients, along with chronic fatigue and anxiety [3]. In addition, depression has been shown to also influence mortality [30]. Some other long-term consequences that have to be taken into consideration are chronic central pain, sexual dysfunction, cognitive impairment, and epileptic syndrome. Due to this multiple possible consequences, the patients' approach should be multidisciplinary, including a neurologist, a psychologist or a psychiatrist, and an occupational therapist [3].

Another important aspect is the risk of recurrence. Cardioembolic strokes or patients suffering from atherosclerosis affecting the large vessels are the ones most at risk for recurrence [3].

2.8 Rehabilitation after stroke

The rehabilitation process of stroke victims is extremely complex. It is not limited only to the medical part of the process, but also includes social, economic, and vocational aspects. It is important to keep in mind that the patient rehabilitation should be achieved through a multidisciplinary approach, with a team of specialists from different domains of activity: physicians, nurses, physiotherapists, speech-language therapists, social workers, and occupational therapists [34].

The methods used for rehabilitation are similar between the young and the elderly. It has been observed that younger people tend to achieve a full recovery after stroke more frequently and more rapidly and require institutionalization less frequently than older patients. The main predictors of full recovery after stroke are age and stroke severity. On the other hand, younger patients struggle more with adjustment issues, family stress, vocational issues, and depression. For this reason, rehabilitation in younger people should focus on issues regarding disease acceptance and community integration. It is of uttermost importance for these patients to be informed about their disease, about possible future consequences, including stroke recurrence. Including these patients in support groups of stroke victims of similar age would also be extremely useful [35].

The rehabilitation program can be performed in acute care hospitals, in different rehabilitation centers, or even at home. In absence of contraindications, rehabilitation should begin as early as possible. Early mobilization, when possible, is also recommended in the first 18–24 hours. The process is individualized depending on patient's disabilities and focuses on improving cognitive, motor, and speech skills. Motor rehabilitation includes different techniques to improve mobility, balance, sit-to-stand, gait, and upper limb function and limit spasticity. Different fitness activities and recreational sports are encouraged in young people since there is a tendency to cease such activities after stroke. Somatosensory rehabilitation and speech therapy should also be included. Acupuncture may be useful for chronic fatigue. Noninvasive brain stimulation (NIBS) helps the process of neuroplasticity [36].

Regarding long-term results, studies show that the beneficial results of rehabilitation programs are maintained up to 1 year after the program is finalized [37].

A more modern and practical rehabilitation method is the StrokeBack project. The rehabilitation process can be done at home and uses telemedicine. The patients first learn the exercises with the help of a physiotherapist and then practice those exercises in the comfort of his own home. The patient's progress is being monitored

and then receives feedback from his caregiver. The method has multiple advantages. Patients are more motivated because they receive constant feedback, and they have the tendency to exercise more, and as a result, their quality of life improves. Another beneficial aspect is that healthcare costs are diminished due to fewer hospital visits. This program would also be helpful especially given the current situation, the Covid-19 pandemic. Patients would still continue their rehabilitation process at home for an indefinite period [38].

2.9 Prevention of stroke in young adults

Primary and secondary stroke prevention is identical both for the young and for the elderly [2]. Prevention focuses primarily on classical cardiovascular risk factors: hypertensions, dyslipidemia, and diabetes. Drug use should be actively discouraged, and a healthy lifestyle promoted: lose weight, exercise regularly, cease smoking, reduce alcohol consumption, and eat more fresh fruits and vegetables [8]. In addition, depending on the etiology, prevention should be individualized and specific measures should be taken.

Another important aspect is raising awareness regarding stroke's most common signs and symptoms. Presentation to hospitals is usually delayed because of improper identification. Patients or bystanders fail to recognize the symptoms and signs of stroke. This is due to the fact that stoke is still considered an illness affecting exclusively the elderly. As a consequence, education programs should be implemented in schools, and awareness campaigns should be created [39, 40].

3. Conclusions

Due to the increasing incidence and the possibility of it leaving long-term consequences, ischemic stroke can be considered a public health concern. Although less suspected in the young, these patients require early identification and must receive rapid medical care. For this reason, awareness campaigns should be developed. People should know that stroke can occur at any age and be aware of its most important signs and symptoms.

The etiology of ischemic stroke in the young differs from that found in the elderly. The possible causes are multiple, including rare genetic ones. But unfortunately, very often, the causes remain unidentified. One possible explanation of this phenomenon is that there are currently no specific guidelines for stroke management in young patients. For this reason, for the diagnosis, treatment, and subsequently secondary prevention of ischemic stroke, a series of universal management guidelines should be developed with priority.

Keeping in mind that stroke occurs at people of young age, with long-life spans ahead, the prognosis of patients after the ischemic event is important to be evaluated. Consequently, developing universal prognosis scores could be extremely valuable. Another particularly important aspect would be determining the risk of recurrence.

Due to increased prevalence of classic cardiovascular risk factors at younger age, physicians should also focus on primary and secondary prevention, actively counseling patients regarding these risk factors, and offer support in their attempt to gradually change their lifestyle. Patients should be advised to give up smoking, exercise regularly, lose weight, rest properly, and reduce alcohol consumption.

Such measures and initiatives should ease the diagnosis process of determining the cause of stroke in young patients, help better manage the case, and reduce the recurrence rate.

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Author details

Diana Mihai[1], Florentina Cristina Plesa[1,2], Any Docu Axelerad[3,4], Alice Munteanu[5], Minerva Claudia Ghinescu[2] and Carmen Adella Sirbu[1,2*]

1 Central Military Emergency University Hospital, Department of Neurology, Bucharest, Romania

2 Titu Maiorescu University, Bucharest, Romania

3 Faculty of Medicine, 'Ovidius' University of Constanta, Department of Neurology, Romania

4 Clinical Emergency Hospital 'St. Apostol Andrei', Constanta, Romania

5 Central Military Emergency University Hospital, Department of Cardiology, Bucharest, Romania

*Address all correspondence to: sircar13@yahoo.com

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