Stoke in young adults

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Introduction

This article includes discussion of stroke in young adults, stroke in the young, and young stroke. The foregoing terms may include synonyms, similar disorders, variations in usage, and abbreviations.

Overview

Current epidemiological data suggest that strokes are occurring at a younger age. As many as 1 out of every 6 strokes occurs in a young adult (18 to 50 years old). Heterogeneity in incidence rates, stroke subtypes, and etiology among younger stroke victims in both developed and developing countries is often noted. Certain historical features and clinical manifestations may occasionally serve as clues toward specific stroke etiologies; nevertheless, determination of etiology, particularly of ischemic stroke in the young, poses many challenges due to a broad array of potential causes, both common and uncommon. In this article, the authors emphasize areas in which the differential diagnosis of stroke and etiologies (including those in pregnancy and puerperium) differs from that in older adults. The authors also note relevant information concerning prognosis of young adults with stroke.

Key points

- Up to 15% of all cerebral infarcts occur in young adults (ages 18 to 50 years).
- Etiologic diagnosis of stroke in young adults requires a different and more complex diagnostic work-up than that of stroke in older adults.
- Overall, cardiac embolism and nonatherosclerotic vasculopathy are the main etiologies of cerebral infarct in younger patients.
- Arteriovenous malformation and arterial hypertension are the main etiologies of cerebral hemorrhages.
- Overall, and despite thorough investigation, the causes of up to one-third of ischemias and hemorrhages remain undetermined.
- Motor recovery is generally better than that of older patients, although a negative impact on multiple cognitive domains may be observed after a long-term follow up.

Historical note and terminology

Information regarding stroke in the younger patient population first began appearing in the literature in the 1950s and 1960s. Interest in this topic has increased due to escalating stroke rates in the younger age group and improvements in patient evaluation. A standardized definition of “young adults” is lacking. People under 40, 45, 50, or even 55 years of age have been classified as young adults. Currently, strokes occurring after adolescence and before the age of 50 are typically considered as occurring in young adults. Although several of the causes of stroke in the young are rare, they account in aggregate for many of the conditions leading to stroke (Kristensen et al 1997; Martin et al 1997; Kittner et al 1998). The incidence of stroke increases sharply after the age of 40, and the spectrum of etiology narrows, with atherosclerosis becoming increasingly common as the risk factors start resembling those in the elderly.

Clinical manifestations

Presentation and course

The symptoms and signs of stroke are directly related to the affected blood vessel (artery or vein), quantity of cerebral
injury, and etiology; there is no apparent relationship to the specific age group affected. As such, a comprehensive history and physical examination (Table 1) are critical to detect the etiology of stroke (Stern et al 1991; Kristensen et al 1997; Martin et al 1997; Kittner 1998; Kittner et al 1998).

**Table 1. Selected Historical Information**

**May suggest a vascular cause:**
- Atherosclerosis
  - Tobacco use
  - Arterial hypertension
  - Hyperlipidemia
  - Diabetes mellitus
  - Prior radiation therapy
  - Homocystinuria
- Dissection
  - Trauma
  - Chiropractic manipulation

**May suggest a cardiac cause:**
- Intravenous drug abuse
- Cardiac murmur
- Splinter hemorrhages
- Deep venous thrombosis
- Association of stroke with exercise or straining
- Valve replacement
- Cancer

**May suggest a hematologic cause:**
- Sickle cell disease
- Deep venous thrombosis
- Livedo reticularis
- History of miscarriages or spontaneous abortions
- Leukostasis
- Asymmetric radial arterial pulses
- Bone marrow transplantation

**Other clues:**
- Recurrent headaches
- Use of hormonal contraceptives
- Papilledema
- Alcohol use
- Recent (within 1 week) febrile illness or systemic infection
- Pregnancy or recent delivery
- **HIV** infection
- Family history of stroke, thrombosis, spontaneous abortion, or premature myocardial infarction
- Hearing loss
- History of uterine or bowel rupture or pneumothorax, suggesting a connective tissue disorder

Adapted from (Stern and Wityk 1994)

**Prognosis and complications**

The prognosis and complications of stroke in young patients are highly dependent on the underlying cause of stroke, as well as the amount and location of CNS damage. The 30-day case fatality is low, particularly in ischemic stroke (0% to 6%), whereas it ranges from 20% to 36% for cerebral hemorrhage (Jacobs et al 2002; Spengos and Vemmos 2010; Groppo et al 2012). The NOMASS data showed that 30-day case fatality rates were higher in blacks and Hispanics than...
in whites (Jacobs et al 2002). Nedeltchev and colleagues found that higher admission NIH Stroke Scale scores, total anterior circulation stroke syndrome, and diabetes mellitus were independent predictors of unfavorable outcome; in their study, 68% achieved a modified Rankin score (mRS) of 0 to 1, 26% had a mRS score of 2 to 5, and 3% were dead by 3 months (Nedeltchev et al 2005). In a large prospective cohort of 968 patients aged 15 to 49 years, outcome at 3 months after first-ever cerebral infarct was found to be favorable (mRS 0-1) in approximately half of the patients, and 80% were functionally independent (mRS 0-2) (Putaala et al 2013). Increasing age, stroke severity, and size of infarct were directly related to unfavorable outcome in this cohort. Moreover, high-density lipoprotein (HDL) levels were inversely correlated with adverse functional outcome (Putaala et al 2013).

In a French study of 287 young adult stroke patients by Leys and colleagues, the mortality rate was 4.5%, and the recurrence rate was 1.4% during the first year, dropping to 1.6% and 1% in the subsequent 2 years, respectively. Myocardial infarction occurred in 0.2% and seizures in 6.6% (Leys et al 2002). Another study found a rate of recurrence of 7.4%, with nearly 90% having a moderate to excellent outcome (Musolino et al 2003). In the Iowa Stroke Registry, mortality was associated with age greater than 25 years and large-artery stroke etiology. In the Iowa study 7% of patients died from the initial stroke, 14% died over a follow-up period of 6 years, 9% had recurrent strokes, 0.4% had subsequent myocardial infarction, and only 49% of young stroke patients were still alive, were not disabled, were without recurrent vascular events, or had not undergone major vascular surgery by the end of the mean 6-year follow-up (Kappelle et al 1994). In a Spanish study of 240 young adult stroke patients (Varona et al 2004), 88% were alive after a mean follow-up of 12.3 years. The average mortality rate was 4.9% in the first year and 0.9% in subsequent years. Recurrent stroke occurred in 3.6% in the first year and 1.7% in subsequent years. Age greater than 35 years, male gender, carotid artery stenosis and the presence of cardiovascular risk factors was associated with worse outcome.

A 4.5% annual rate of symptomatic recurrent cerebral ischemic events (TIA or cerebral infarction) was found in 94 young patients with a follow-up of 48 months, most often in patients with an index cardioembolic infarct, followed by patients with an undetermined cause of infarct and a nonatherosclerotic vasculopathy. A neuroradiological (brain MRI) follow-up was performed 48 months after the index event in all 94 patients. Silent cerebral infarcts (lacunes) were documented in 9.5% of patients, mostly in patients with embolism from a cardiac source and undetermined cause of stroke (Patella et al 2011).

In a cohort of 250 young patients with cerebral infarct with a mean follow-up period of 52 months, the estimated 10-year survival rate was 86% and the probability of composite vascular events (recurrent stroke, vascular death, and myocardial infarction) was 30.4%. Heart failure and initial stroke severity were the leading independent predictors of mortality. Men tended to have a lower survival rate and higher risk of composite vascular events than women (Spengos and Vemmos 2010).

Aarnio and colleagues studied long-term mortality and stroke recurrence in first-ever ischemic stroke for patients aged 15 to 49 years (mean follow-up of 10.2 ± 4.3 years) (Aarnio et al 2014). They found a 15.7% mortality rate (cumulative risk, 23.0%; 95% CI 19.1-26.9) and a 13.6% recurrent stroke rate. The most important risk factor for mortality after first-ever ischemic stroke was recurrent stroke (hazard ratio, 16.68; 2.33-119.56). Observed mortality was 7-fold higher than the expected mortality (standardized mortality ratio, 6.94; 95% confidence interval, 5.84-8.04) and particularly high among patients who experienced a recurrent stroke (standardized mortality ratio, 14.43; 95% confidence interval, 10.11-18.74) (Aarnio et al 2014).

Young adult patients with stroke remain at substantial risk of vascular recurrence in the long-term after an index event. After a mean follow-up of 9.1 years, one fifth of 724 consecutive patients with a first-ever transient ischemic attack, cerebral infarct, or intracerebral hemorrhage experienced at least 1 incident vascular event (stroke, myocardial infarction, or cardiac or peripheral arterial revascularization procedures) (Rutten-Jacobs et al 2013). The risk of any vascular recurrence was highest in the year following the index transient ischemic attack or cerebral infarct. In young adult patients with a cerebral infarct as index event, the 20-year cumulative stroke risk (19%) or any vascular event (33%) was higher compared with those patients with an initial transient ischemic attack or intracerebral hemorrhage. According to subgroups of TOAST criteria, the higher 20-year cumulative stroke recurrence risk was observed in patients with initial lacunar infarct (30%), whereas the atherothrombotic and cardioembolic stroke subgroups each had a 20-year cumulative stroke recurrence risk of 24%, and in patients with infarct of undetermined etiology the 20-year cumulative stroke recurrence risk was 12% (Rutten-Jacobs et al 2013).

Pezzini and associates followed 1867 patients with first-ever ischemic stroke (18 to 45 years of age) for a median of 40
months (Pezzini et al 2014). They found 163 patients to have recurrent thrombotic events (average rate, 2.26 per 100 person-years at risk). The 10-year cumulative risk of these events was estimated at the level of 14.7% (95% CI; 12.2%-
17.9%). The cumulative risk for brain ischemia was 14.0% (95%CI; 11.4%-17.1%) and 0.7% (95% CI; 0.4%-1.3%) for myocardial infarction or other arterial events. The independent predictors of recurrent thrombotic events were familial history of stroke, migraine with aura, circulating antiphospholipid antibodies, discontinuation of antiplatelet and antihypertensive medications, and any increase of 1 traditional vascular risk factor (Pezzini et al 2014). Young adults with a previous transient ischemic attack have a 20-year cumulative risk of stroke of 17% and a 28% risk of any vascular event. Young adults with intracerebral hemorrhage exhibited the lowest risk of stroke recurrence (10%) and of any vascular event (11.6%) (Rutten-Jacobs et al 2013).

In a Swedish cohort of 17,149 patients aged 18 to 54 years who survived a first cerebral infarct from 1987 to 2006, patients were stratified into four 5-year periods according to their admission period (the reference period and the last period were 1987 to 1991 and 2002 to 2006, respectively) (Giang et al 2016). In 14% of patients (2,432), a recurrent cerebral infarct occurred within 4 years of follow-up. The cumulative 4-year risk of recurrence was higher in men than in women (with rates of 11.8% and 9.8%, respectively) during the 2002 to 2006 period. During the study period, the 4-year risk of recurrence decreased by 55% in men and by 59% in women. The highest risk of recurrence occurred within the first year after the index event and decreased thereafter, with an estimated annual recurrence rate of 2% from 2002 to 2006. Moreover, a decreasing trend in stroke recurrence over time was observed in all age groups except in patients aged 18 to 25 years.

In a prospective cohort study by Arntz and colleagues of 656 patients aged 18 to 50 years with a first lifetime ischemic stroke – out of whom 209 patients had a transient ischemic attack – and a mean follow-up of 12.4 years (21% of patients had a follow-up of more than 20 years), one third (197) of the patients had at least 1 more ischemic event (Arntz et al 2016). In this cohort, the 25-year cumulative risk for recurrent cerebral infarct was 30%, and for any ischemic event (transient ischemic attack or ischemic stroke), it was 45%. There were no differences in the 25-year cumulative risk of cerebral ischemia attributable to gender or to age category. Patients who had the first ischemic stroke due to cardioembolism or small-vessel disease had a higher 25-year cumulative risk than patients with "stroke of undetermined etiology" according to TOAST criteria, with rates of 50.8%, 37.5%, and 22.9%, respectively. Poor kidney function (eGFR < 60), smoking, history of peripheral arterial disease, and cardiac disease were independently associated with recurrent ischemic events (Arntz et al 2016). Moreover, in a cohort of 619 patients with ischemic stroke aged 18 to 50 years, 45% of patients had a poor functional outcome (modified Rankin scale ≥ 2), whereas 23% were still dependent in daily life (Instrumental Activities of Daily Living Scale < 8). Women had a 2- to 3-fold higher risk of poor functional outcome (Synhaeve et al 2016).

Data about mortality after intracerebral hemorrhage are scarce. In a Finnish retrospective cohort, the mortality rate in 325 patients from the ages of 16 to 49 years with a first-ever nontraumatic intracerebral hemorrhage was 17% at 3 months. A higher 3-month mortality rate was associated with higher National Institutes of Health Stroke Scale scores, infratentorial hematoma location, and multiple hemorrhages. This observational study showed a lower mortality rate for patients undergoing surgical evacuation of hematoma than for those receiving conservative treatment (Koivunen et al 2014).

Although the incidence of stroke in young adults is low and the outcome and prognosis generally favorable as compared to the older population, the impact of stroke is much higher in the former with even minor residual deficits resulting in substantial loss of economic productivity and severe emotional or social sequelae that impair quality of life. In the Iowa study, only 42% of patients were able to resume work, and the majority reported emotional, social, or physical residuals that impacted quality of life (Kappelle et al 1994). In the study by Leys and colleagues, favorable outcome (mRS 0-2) was observed in 94%; however, 4.2% lost their job despite achieving a mRS score of 0 to 1. The emotional, social, and physical problems affecting young stroke patients have also been emphasized by another study (Neau et al 1998). Patients with strokes of unknown cause, however, do seem to have the lowest risk of stroke recurrence, with a relative risk of 0.1 compared to those with known cause (Kappelle et al 1994).

A nearly 12-year follow-up of a retrospectively selected cohort of patients with brain infarction at a young age (mean age of 41 at index event) showed the worst prognosis compared with matched controls by sex and age. Thus, 77% of 187 young stroke patients had a 2-fold higher rate of depression, anxiety, and sleeping problems compared to a control population, whereas memory deficit was 8 times higher in stroke patients as compared with controls. Also, young stroke patients were less able to handle full-time work compared with controls (Waje-Andreassen et al 2013).
Furthermore, in the last year, data of cognitive performance after a longer follow-up have been reported in a prospective cohort of 277 young patients with a mean age of 40 at index infarct (56% women, mostly with a good outcome according to the Barthel Index at follow-up) having a first-ever ischemic stroke, compared with a matched stroke-free population (146 controls) (Schaapsmeerders et al 2013). The median follow-up was 11 years and almost half the patients had a follow-up of over 10 years. Compared with matched controls, up to 50% of young stroke patients exhibited below-average cognitive performance or impairment in processing speed, executive functioning, attention, working, and immediate and delayed memory. Regarding the location of index stroke, patients with supratentorial infarct on the left side had the worst cognitive outcome (Schaapsmeerders et al 2013).

Long-term cognitive outcomes in young ischemic stroke patients (n = 96; median age at index event 43.0 years; 45.8% male) were studied by de Bruijn and colleagues (de Bruijn et al 2014). This study excluded patients with severe aphasia or preexistent cognitive impairment. Visual perception, visual and verbal memory, mental speed, and executive functioning were assessed and compared to controls with adjustment for education level. The authors found that the patients performed significantly worse than controls in mental speed tests (Stroop Color-Word Test Part 1 and Symbol-Digit Substitution Task), and verbal memory assessments (Word Pair test). These data confirm long-term cognitive impairment in this patient population (de Bruijn et al 2014).

Seizures within 7 days of ischemic stroke (acute symptomatic seizures) occurred in 3.5% of 995 young patients (ranging in age from 15 to 49 years) with a first-ever ischemic stroke included in a retrospective observational cohort (Roivainen et al 2013). Nearly 60% of seizures occurred in the first 24 hours after stroke onset. Anxiolytic use, moderate stroke severity, cortical involvement, and hyponatremia at the time of index stroke were independently associated with a higher risk of acute symptomatic seizures. In addition, in the same cohort at 5 years after index infarct, 1 out of 10 young ischemic stroke patients developed late poststroke seizures (7 days from brain infarct; patients with previous epilepsy were excluded). Total or partial anterior circulation infarct (Bamford criteria), history of acute symptomatic seizures, hemorrhagic infarction, antidepressant use at the time of late poststroke seizures, male gender, and hyperglycemia were independently associated with a higher risk for late poststroke seizures (Roivainen et al 2013).

The risk of poststroke epilepsy (7 days after the initial event) was reported in another cohort of around 700 young adult stroke patients (mean age of 40.5, ranging from 18 to 50), 60% with cerebral infarct, 10% with intracerebral hemorrhage, and the remainder with a transient ischemic attack (Arntz et al 2013). In this series, 11% developed epilepsy after a mean follow-up of 9 years and 6% developed epilepsy with recurrent seizures, mainly within the first 12 months after the stroke. The first poststroke seizure was tonic-clonic generalized in one-third of patients and simple partial in another third of patients. The highest risk of epilepsy was observed in patients with intracerebral hemorrhage (17%), followed by patients with cerebral infarct (14%), and the lowest risk was observed in patients with transient ischemic attack (3%). Cumulative risk of both poststroke epilepsy and epilepsy with recurrent seizures was higher in patients with intracerebral hemorrhage as compared to the other stroke subtypes. A high NIHSS score at admission was found to be a predictor of poststroke epilepsy and epilepsy with recurrent seizures (Arntz et al 2013).

Clinical vignette

Vignette 1. A 33-year-old man had acute onset of right-sided numbness and weakness with associated speech disturbance. He had been complaining of a pressure-type headache behind the left eye and neck discomfort for the past 10 days following a strenuous football practice. He was otherwise healthy with an unremarkable personal history. He did not use tobacco or illicit drugs and occasionally drank alcohol.

Neurologic examination revealed word-finding difficulties, left Horner syndrome, mild right central facial weakness, right hemiparesis, decreased sensation over the right hemibody, and an upgoing toe on the right.

Blood count, electrolytes, coagulation profile, and metabolic panel were within normal limits. Urine toxicology screen was negative. Initial cranial CT was negative. Echocardiogram was normal. MRI of the head showed an area of restricted diffusion in the left subcortical frontal lobe. MRA of the head was normal; MRA of the neck showed a cervical left internal carotid artery dissection extending 1.5 cm rostrally with significant luminal narrowing. He was anticoagulated with intravenous unfractionated heparin and was subsequently switched to warfarin therapy. A 3-month follow-up MRA showed recanalization of the left internal carotid artery. He was then switched to aspirin 325 mg daily. He remains asymptomatic.
Vignette 2. A 39-year-old woman with migraine without aura on oral contraceptives presented with a sudden-onset “worst headache of her life” with presyncopal episodes and right hemibody numbness and hemiparesis. She had 2 generalized tonic-clonic seizures on the date of admission and was loaded with intravenous valproic acid. Neurologic examination revealed right upper extremity pronator drift and mild right upper extremity weakness. Head CT without contrast demonstrated mild Sylvian fissure/temporo-occipital and left frontal convexity subarachnoid hemorrhage. There was hyperdensity in the superior sagittal sinus. CT angiography revealed absence of contrast enhancement in nearly the entire superior sagital sinus, right transverse and sigmoid sinuses, and right internal jugular vein. No perfusion deficits were noted, although there was mild vasospasm of the M2 segment of the right MCA. Angiography demonstrated filling defects in the above vessels and in numerous bilateral paramedian frontoparietal cortical veins.

Lupus-sensitive activated partial thromboplastin time (aPTT) was mildly prolonged. There was no evidence of lupus anticoagulant or antiphospholipid antibody, however. Protein C & S levels, antithrombin, factor V Leiden mutation, activated protein C resistance, and prothrombin 20210A gene mutation were unremarkable. C-reactive protein was elevated (33.56 mg/L), and erythrocyte sedimentation rate was mildly elevated (21 mm/hr). Homocysteine was low (2.2 mcmol/L). Pregnancy screen and human immunodeficiency virus test were negative. Fasting lipids, complete blood count, antineuronal nuclear antibody, and rheumatoid factor were normal.

She was anticoagulated with heparin and started on Lovenox as a bridge to warfarin therapy. Mild right upper extremity pronator drift persisted at discharge. She was placed on levetiracetam and had no further seizures. A plan was made to repeat the lupus anticoagulant and antiphospholipid antibodies at 12 weeks.

Vignette 3. A right-handed, 16-year-old Hispanic woman living in a coastal rural community was admitted to the hospital 5 days after the sudden onset of an excruciating, throbbing left occipital headache, nausea, vomiting, and reduced level of consciousness. Five months before, she had been diagnosed with a molar pregnancy at 12 weeks of gestation, requiring dilatation and evacuation. She had no history of alcohol abuse, illicit drugs use, cranial trauma, or hematological disease; she was given no follow-up procedure after the early termination of this first pregnancy.

At hospital admission, her systemic examination was unremarkable. The neurologic examination showed an agitated and confused patient whose pupils were symmetric and responsive to light. Direct funduscopic examination was normal. No motor deficit was noted, and meningeal signs were present.

Coagulation screening was normal. Serum human chorionic gonadotropin levels were over 10,000 UI/ml. An initial noncontrast cranial CT showed a large left parietal hematoma involving the grey and white matter surrounded by a severe perilesional edema and ipsilateral intraventricular extension. Pelvic and pulmonary metastases were detected by pelvic ultrasonography and CT of the thorax, respectively. A brain MRI with and without contrast disclosed a large left parietal hematoma with intraventricular extension and severe perilesional edema. A small, ill-defined hyperintense lesion was also observed on the contralateral parietal lobe.

A diagnosis of intracranial bleeding due to metastatic choriocarcinoma was established, and the oncology department planned to start intravenous chemotherapy. Nevertheless, her condition deteriorated over the course of the next 3 days. A second noncontrast CT scan showed a large bilateral hematoma in both parietal lobes. She was progressively unresponsive and then died. An autopsy was not performed.

Biological basis

Etiology and pathogenesis

Stroke in the young usually results from a variety of conditions that, although individually uncommon, collectively account for approximately 40% of all strokes. Ischemic strokes can be caused by atherosclerotic cerebrovascular disease, nonatherosclerotic abnormalities, cardiac emboli, hematologic or coagulation disorders, substance abuse, migraines, oral contraceptive use, inflammatory disorders, and many other conditions. The spectrum of etiologies may differ by geographic region (Ghandehari and Moud 2006), with traditional stroke etiologies reportedly higher in eastern countries (Razzaq et al 2002; Mehndiratta et al 2004). The etiology and risk factors of ischemic stroke after the age of
40 is similar to those seen in older patients (Putaala 2009). The frequency of etiologies of cerebral infarct in the young may differ according to the classification system used. Thus, based on the widely used TOAST classification system, the main etiologies in a series of 104 patients aged 18 to 45 were cardiac embolism (21%) and “other causes” (19%), whereas large atherothrombotic arteriopathy and small vessel disease each accounted for 10% of etiologies. In this cohort, the etiology of 40% of the cerebral infarcts could not be determined (Chatzikonstantinou et al 2012).

In a prospective cohort study on Caucasian patients aged 18 to 50 years with a first-ever stroke, 656 patients had ischemic stroke (31% transient ischemic attack); the mean age was 40.7 years, 79% were older than 35, and 47% were men. According to TOAST criteria, large-artery disease was significantly more common in patients over 35 years than in those below that age (11.6% vs. 2.9%, respectively). The rate of cardioembolic source was quite similar between the 2 age groups: 13.5% and 11.6% in those over and those under 35 years, respectively. Small-vessel disease was more common, although not significantly, in individuals over 35 years (11% vs. 6%). Ischemic stroke classified as “other defined etiology” was significantly more frequent in patients under 35 years (23%) than in the older patients (12%). The etiology of stroke remained undetermined in nearly half of the patients under 35 years and in one third of those over that threshold (van Alebeek et al 2017).

In a large cohort of 3331 patients between the ages of 15 and 50 with a first-ever cerebral infarct assessed according to TOAST criteria at 15 European stroke centers, stroke of other determined etiology was the most common subgroup (22%), followed by cardioembolism, found in 17% of the patients (Yesilot Barlas et al 2013). In the subgroup of other determined etiology, cervical artery dissection (13%) was the main cause, followed by genetic thrombophilia and systemic vasculitis. In the cardioembolism subgroup, atrial fibrillation or flutter was the most common high-risk source of embolism, whereas patent foramen ovale was the most frequent low-risk source of embolism. Small-vessel occlusion and large-artery disease were found less frequently, accounting for 12% and 9% of etiologies, respectively. Etiology of ischemic stroke could not be determined in 40% of the patients (Yesilot Barlas et al 2013). Compared by gender, the most common TOAST subgroup in females was “other determined etiology” (24%), mostly involving cervical artery dissection (13%) and nonatherosclerotic inflammatory arteriopathies (systemic vasculitis), whereas small-vessel occlusion (15%) and nonatherosclerotic, noninflammatory arteriopathies (mainly cervical artery dissection) were the most common TOAST etiological subgroups in males. The proportion of strokes of undetermined etiology was larger in females (43%) than in males (37%) (Yesilot Barlas et al 2013).

In a cohort of 511 patients between 18 and 49 years of age (mean age of 39.8), most of whom were being seen for a first-ever stroke, no significant differences were found between females and males as to the proportion of small- and large-vessel disease, prothrombotic states, cervical arterial dissection, and stroke of undetermined etiology, although cardioembolism and substance abuse predominated in men as compared with women (Nakagawa and Hoffmann 2013). Moreover, 44% of young stroke patients (and almost 60% of the women) had nontraditional etiologies for stroke, including prothrombotic states, migraine-related conditions, substance abuse, cervical artery dissection, cerebral venous thrombosis, inflammatory and miscellaneous vasculopathy, and pathological conditions occurring either exclusively (related to pregnancy and postpartum) or more frequently in women (fibromuscular dysplasia and Moyamoya syndrome) (Nakagawa and Hoffmann 2013).

In a population-based study of a cohort of 950 patients aged 16 to 49 years, differences in ischemic stroke subtypes according to TOAST criteria were found between African-Americans and European-Americans (Trivedi et al 2015). In young African-American patients, cardioembolic stroke (19%) and lacunar infarcts (18%) predominated over other etiologies, and one-half of the infarcts were considered to be cryptogenic. In European-American patients, cardioembolic stroke was the most common etiology (19%), followed by lacunar infarcts (13%); the etiology of infarct could not be determined in 52% of patients. Young African-American patients, particularly those over the age of 40, were found to be 1.6 times more likely to have an infarct due to small-vessel disease than similarly aged European-Americans when compared with all other subtypes combined. Patients over the age of 40 years were 3 times more likely to have either large-artery disease or lacunar infarct, whereas patients younger than 40 years of age had 1.6 times more risk of a cardioembolic infarct. Large-artery and small-vessel disease – with frequencies of 43% and 16%, respectively – were the most common etiologies in 1395 Chinese patients aged 18 to 50 years (mean age 38.5; 79% men). Cardioembolism accounted for 6% of all cerebral infarcts, and patent foramen ovale made up 59% of cardiac sources of embolism. One in 10 patients with cerebral infarct in this cohort had multiple potential causes of stroke, whereas the etiology was undetermined in 15% of patients (Li et al 2017).

In a secondary analysis of data from a prospective multicenter study in 15 European countries in the last few months,
a comparison was done of the anterior- and posterior-circulation ischemic stroke etiologies, according to TOAST classification, in 2101 patients aged 18 to 50 years (von Sarnowski et al 2017). One third (612) of these patients had a posterior circulation cerebral infarct (86% were unilateral and 50% were in the cerebellum). Large-artery disease (22%) and cardioembolism (18%) predominated in patients with anterior circulation stroke, whereas in patients with posterior circulation stroke these etiologies accounted for 15% each. Small penetrating artery disease was noticeably more common in posterior (15%) than in anterior (12%) circulation infarcts. Infarcts classified as “other determined etiology” were more common in patients with posterior circulation stroke (25%) than in those with anterior circulation stroke (16%). Cervical artery dissection was twice as common in patients with posterior circulation strokes (17%) as in those with anterior circulation strokes (8%). Patent foramen ovale was more common in posterior circulation stroke (31%) than in anterior circulation stroke (25%). In both arterial territories, the cause of one third of strokes remained undetermined (von Sarnowski et al 2017).

On the other hand, using the ASCO system, which introduces a complete stroke phenotype classification (stroke etiology and the presence of all underlying diseases, divided by grade of severity), the proportion of small vessel disease in the same cohort was no different in comparison to the TOAST system, whereas the frequencies of large vessel disease, embolism from a cardiac source, and other etiologies were lower compared to the TOAST criteria, with 8.7%, 10.6%, and 13.5%, respectively. The rate of stroke of undetermined cause (“cryptogenic strokes”) using the corresponding score in the ASCO system (A0S0C0O0) was half that of the TOAST system (19%) (Chatzikonstantinou et al 2012). Jaffre and coworkers identified a definite cause of stroke based on the ASCO classification system (grade 1) in half of 400 patients aged 16 to 54 (mean age 44.5; 39% under 44) with a first cerebral infarct. Atherosclerosis and other definite causes (mainly carotid and vertebral arterial dissections) accounted for 18% and 16% of cases, respectively; cardioembolism (9%) and small vessel disease (7%) were less common etiologies (Jaffre et al 2014).

Hemorrhagic strokes may be caused by underlying vascular structural abnormalities, abnormal composition of blood vessels, effects of chronic arterial hypertension, trauma, or effects of acute hypertension and vasoconstriction, such as in the setting of sympathomimetic or illicit drug use. The cause of up to one-third of hemorrhages may remain unknown even after an exhaustive evaluation, especially in those aged 40 to 49 years (Awada et al 1996; Lai et al 2005; Koivunen et al 2015). A notable genetic study found that polymorphisms in the glutathione peroxidase (Gpx-3) gene, perhaps via interactions with conventional vascular risk factors, increase the risk for ischemic stroke in children and young adults (Voetsch et al 2007). Such polymorphisms affect the gene's transcriptional activity and thereby compromise plasma antioxidant and antithrombotic activities. Arterial hypertension and arteriovenous malformations were the leading causes in 69 patients with a first-ever intracerebral hemorrhage included in a prospective study aimed at assessing the consequences of stroke in the young. Etiology could not be determined in nearly 20% of these patients and 18% had an incomplete evaluation, mainly because of early death (Rutten-Jacobs et al 2013). In 1 study, arterial hypertension and vascular malformations (mainly cavernous angiomas) were found to be the leading etiologies - each accounting for 25% of cases - in a large retrospective cohort of nontraumatic intracerebral hemorrhage. Cerebral vein thrombosis and illicit drug use were the most common etiologies in patients younger than 30, whereas structural lesions (arteriovenous malformations and cavernous angiomas) and hypertensive microangiopathy were the main etiologies in the over-30 group. In a retrospective study of 1,706 patients with acute intracerebral hemorrhage, 42 (2.5%) had cavernous malformations (confirmed by pathological examination), and 10 (0.6%) had a developmental venous anomaly (stellate or linear vascular lesions converging into a collecting vein with a caput medusae-like appearance after enhancement on brain MRI). The mean age of the 42 patients with cavernous malformations was 37 years, and the mean hematoma size was 2 centimeters; 48% of hemorrhages (20) were located in the brainstem, mainly in the pons, and one-third were located in the cortex. In the 10 patients with developmental venous anomalies, the mean age was 31 years; 6 hematomas were located in the cerebellum, 2 in the brainstem, and the remainder were supratentorial with a mean hematoma size of 1.8 centimeters (Li et al 2016).

Ischemic stroke can be due to embolism from cardiac or arterial sources, from cervicocephalic arterial dissections, or from primary atherosclerotic lesions occluding large or small arteries. In situ thrombosis in a cerebral vessel can also develop as a result of a hypercoagulable state. Hemorrhagic strokes develop due to rupture of vascular abnormalities, such as aneurysms or vascular malformations. Significantly elevated blood pressure classically results in subcortical, brainstem, cerebellar, or lobar hemorrhages.

Epidemiology**

Worldwide, incidence of stroke in infants and young children is reported to be from 3 to 13 cases per 100,000, with a
recurrence rate of 6% to 40% (Giroud et al 1995; Strater 2002; Roach et al 2008). Annual stroke incidence in individuals aged 15 to 45 varies greatly, depending on how estimates are derived, but appears to range from 5.83 to 12.1 cases per 100,000 persons (Kristensen et al 1997; Marini et al 2001; Groppo et al 2012). In developed Western countries, up to 13% of first-ever ischemic strokes occur in people younger than 45 years of age (Bogousslavsky et al 1988; Bogousslavsky and Pierre 1992; Nedeltchev et al 2005; Rasura et al 2006), whereas this age group may account for 20% to 30% of first-time strokes in developing countries (Radhakrishnan et al 1986; Al Rajeh and Awada 2002). The incidence of ischemic stroke ranges from 4/100,000 to 47/100,000 in those 25 to 34 years of age, and from 9/100,000 to 93/100,000 in those 35 to 44 years of age in the European population (Truelsen et al 2006). In the United States, the ethnic composition of the population may produce differences in reported stroke incidence among young individuals; the Baltimore-Washington Cooperative Young Stroke Study reported an annual cerebral infarction incidence of 10.55 per 100,000 Caucasians and 21.7 per 100,000 African Americans (Kittner et al 1993).

For intracerebral hemorrhage, the rate for whites was 3 per 100,000 and for African Americans was 9 per 100,000 (subarachnoid hemorrhage 60% and intracerebral hemorrhage 40%). The population-based Northern Manhattan Stroke Project study found incidence rates for stroke in the young of 23 per 100,000 persons (10 for infarct, 7 for intracerebral hemorrhage, and 6 for subarachnoid hemorrhage). The risk was more than 2-fold higher for blacks and Hispanics as compared with whites (Jacobs et al 2002). These urban and suburban North American population studies, however, found incidences somewhat higher than other studies. To put this entity into perspective, stroke in this age group is reportedly twice as prevalent as multiple sclerosis in 18- to 44-year-old persons (Collins 1997). Although the overall male:female ratio is equal between the ages of 15 and 45 years, females predominate if the age is restricted to below 30 years (Rasura et al 2006; Spengos and Vemmos 2010). This correlates with childbearing years when the risk is predominantly for hemorrhagic stroke. Based on a retrospective cohort of 336 patients aged 16 to 49 years (median age of 42) with a first-ever nontraumatic intracerebral hemorrhage, an annual incidence in the young was estimated at 4.9 per 100.00, with higher rates in males (6.2) than in females (4.0) (Koivunen et al 2015).

**Prevention**

Stroke prevention is of paramount importance in young individuals because of its high impact on productivity and future quality of life. Unfortunately, no single preventative measure can reduce the general risk of stroke in young adults. As many risks are modifiable, general prevention strategies (as in the older population) may lessen the impact of stroke in this population. A risk factor study found diabetes (odds ratio 11.6), hypertension (odds ratio 6.8), heart disease (odds ratio 2.7), current tobacco use (odds ratio 2.5), and long history of alcohol use (odds ratio 15.3) to be risk factors in patients aged 15 to 45 years with first onset stroke (You et al 1997). Neither heavy alcohol use just prior to stroke or history of oral contraceptive use was associated with an increased risk of stroke in this study. Tobacco use, elevated triglycerides, and alcohol abuse were more common in men whereas migraine was more frequent in women. Arterial hypertension and elevated cholesterol and triglycerides are more common in patients older than 35 years. In patients below 35 years, oral contraceptive use is more prevalent (Carolei et al 1993). Tobacco use and arterial hypertension were especially noted in young African-American patients (Rohr et al 1996). The amount and type of alcohol can influence stroke risk, with light to moderate alcohol consumption reducing stroke risk in young women (Malaracher et al 2001).

In general, reduction of modifiable risk factors is the single best preventative action to lessen strokes in both younger and older individuals (Ning and Furie 2004). Primary stroke prevention guidelines recommend regular screening and appropriate treatment of hypertension and diabetes, smoking cessation for all current smokers, weight reduction in overweight persons, a healthy diet, and regular exercise (Furie et al 2011). No similar recommendations have been specifically directed at the younger stroke patient population (Meschia et al 2014). It is recommended that female sufferers of migraine, particularly with aura, stop smoking and replace hormonal contraception (especially those containing estrogen) with other methods. Attempting to reduce migraine frequency through treatment, particularly in the case of the aural type, may be a reasonable step, although there is no evidence that this will reduce stroke occurrence (Meschia et al 2014). Patients with a history of stroke related to drug abuse (cocaine and amphetamines) should be referred to an appropriate therapeutic program. Treatment of Fabry disease with enzyme replacement therapy has not proven to reduce stroke risk (Meschia et al 2014).

In a retrospective Norwegian study, the risk of recurrent stroke or myocardial infarction was proportional to the number of risk factors, being as high as 30% with 4 risk factors and 67% with 5 risk factors, and as low as 2.1% in patients with no risk factors (Naess et al 2005). The authors suggest that long-term stroke preventive measures may
not be warranted in young stroke patients with no identifiable risk factors. Risk factor control can be challenging in the young population: in the French PFO-ASA study, greater than 50% to 60% of young stroke patients continued smoking or had poorly controlled blood pressure after their stroke (Arquizan et al 2005). Prevention has a major role in a few diseases that predispose to stroke in the young: for example, timely blood transfusions have been shown to reduce the risk for stroke in patients with sickle cell disease (Adams et al 1998b). It was also shown that periodic red cell transfusion (target reduction of hemoglobin S to less than 30%) has been shown to effectively reduce the risk for stroke in patients with sickle cell disease (Meschia et al 2014). A history of illicit and licit (including over-the-counter) drug use should be sought during patient encounters and appropriate counseling initiated as needed. Caution has also been recommended in women using oral contraceptives with additional risk factors (cigarette smoking or prior thromboembolic events) in the setting of migraine (Bousser et al 2000).

As has been stated previously, the burden of stroke is increasing among the young worldwide. In a comprehensive review of stroke in young adults and adolescents, Singhal and colleagues emphasized the need to implement educational, preventive, and support strategies, particularly in high-risk groups and young stroke survivors and their families (Singhal et al 2013). They also highlighted the need to promote research on the topic of stroke in young adults to gather reliable epidemiological data and provide feedback for planning and service delivery by stroke professionals and policymakers (Singhal et al 2013).

Investment in research and educational campaigns on this topic may be insufficient or negligible in countries with middle- and, particularly, low-income economies where other health problems are considered priorities. Nevertheless, these countries can benefit from successful educational strategies, stroke survivor support experiences, and prevention and rehabilitation interventions targeted at young adults with stroke that have been developed in high-income economies but are adaptable to local facilities.

**Differential diagnosis**

Conditions that can simulate stroke include focal seizures, migraine with prolonged aura, and migraine variants such as basilar and hemiplegic migraines, acute vestibular syndrome, hypo- and hyperglycemia, periodic paralysis, multiple sclerosis, brain tumor, subdural hematoma, cerebral contusion, encephalitis, radiculopathy, neuromuscular junction disorders, neuropathy, Wernicke encephalopathy, and conversion disorder (Singhal et al 2013). A detailed history, physical exam, and appropriate laboratory or neuroimaging tests should be performed to further evaluate for these stroke mimics.

Defining the cause of stroke in a 15- to 45-year-old patient is often challenging because of the broad spectrum of etiologies to be considered. Published studies of ischemic stroke in the young attribute variable percentages to several stroke etiologies. An overview suggests that the cause of stroke is large artery atherosclerosis in 0% to 63% of patients, nonatherosclerotic disease in 3% to 33%, small vessel disease in 2% to 21%, cardiac embolism in 5% to 37%, hematologic disease in 3% to 28%, oral contraceptives in 3% to 24%, drug abuse in 2% to 11%, and migraine in 2% to 18% of patients. In 4% to 56% of patients, the etiology remains undefined. Significant variability in the proportion of strokes attributed to any 1 cause is related to the population used to collect the data (community-based vs. tertiary care center) as well as the extent and availability of diagnostic evaluation. Multiple stroke etiologies may coexist.

A report including cases from both community and referral hospitals determined etiology percentages from Baltimore City and regional counties: cardiac 15.4%, small vessel disease 9.8%, hematologic 8.9%, nonatherosclerotic vasculopathy 5.6%, substance abuse 4.7%, oral contraceptive use 2.6%, large artery atherosclerosis 1.9%, migraine 0.7%, and cryptogenic 31.8% (Kittner et al 1998). Transesophageal echocardiography was not readily available, possibly accounting for the relatively high percentage of strokes without a definable cause. A Swedish population-based epidemiological survey of stroke in the young found the following frequencies of etiologies: cardiac 33%, nonatherosclerotic vasculopathy 19%, atherosclerotic 11%, hematologic 7%, oral contraceptive use 3%, migraine 1%, and cryptogenic 21%. Transesophageal echocardiography was more available in this study (Kristensen et al 1997). Cardioembolism, mainly from patent foramen ovale and cardiomyopathy, accounted for approximately half of cerebral infarcts in 215 patients 18 to 45 years of age who were evaluated in a tertiary stroke center. One-third of the patients had “other determined causes,” according to TOAST criteria, mainly comprising arterial dissection (13%), reversible cerebral vasoconstriction syndromes (5%), moyamoya disease (3%), and hypercoagulable state (2.8%). Atherosclerotic small-vessel and large-vessel disease were found in 7% and 2% of the patients, respectively, and occurred exclusively in patients older than 36 years of age. Probably because of extensive diagnostic workup, the cause remained undetermined in only 9% of the patients in this cohort (Ji et al 2012).
Atherosclerosis occurs in patients with predisposing risk factors and increases in a linear fashion with advancing age (7% to 30% incidence in patients younger than 50 years). Atherosclerosis as a cause of stroke is less prominent from the 15- to 30-year age group (2%) and more prominent in the 30- to 45-year age group (30% to 35%) (Bogousslavsky and Regli 1987; Carolei et al 1993).

Physicians should avoid attributing atherosclerosis as the etiology of stroke in young patients simply because risk factors are present; nevertheless, with the growing prevalence of obesity, diabetes, and metabolic syndrome, atherosclerosis is increasingly being recognized as the cause of stroke in children and young adults. In fact, large artery atherosclerosis (mostly diagnosed by angiography and ultrasound examination) was the most common cause of stroke in 197 Chinese young adults with cerebral infarct (mean age of 39), accounting for 41% of all stroke etiology, followed by other causes in a quarter of those patients (Niu et al 2014). Intracranial atherosclerotic disease predominated in the same young patients with large artery atherosclerosis, which involves the carotid circulation (middle cerebral artery and intracranial internal carotid artery) in approximately 70% of cases. Almost all patients with intracranial atherosclerotic disease had multiple modifiable stroke risk factors, with stroke due to large artery atherosclerosis increasing in proportion to the number of stroke risk factors (Niu et al 2014). Nonatherosclerotic vasculopathy is a heterogeneous category that may account for 14% to 25% of stroke in younger patients (Biller et al 1991; Rasura et al 2006). Disorders in this category include focal cerebral arteriopathy (FCA) of childhood, Takayasu disease, fibromuscular dysplasia, cervical carotid and vertebral dissections, idiopathic or secondary forms of moyamoya disease, peripartum angiopathy, reversible vasoconstrictive syndromes, radiation-induced arteriopathy, non-amyloid vasculopathy, hyperhomocysteinemia, and others. In the International Pediatric Stroke Study, arteriopathy was identified on neurovascular imaging in 53% of children with arterial ischemic stroke (Amlie-Lefond et al 2009). FCA was the most common type (25%), followed by moyamoya disease and syndrome, and arterial dissection. Recent upper respiratory tract infection was found to be a predictor for FCA, especially in children 5 to 9 years of age. The clinical-imaging features of primary cerebral vasculitis in young adults appear similar to the features of primary cerebral vasculitis in children, which have been described (Aviv et al 2006; Benseler et al 2006).

Fibromuscular dysplasia is the most frequent arterial dysplasia of the vertebral and carotid vasculature, typically affecting medium-sized arteries of young Caucasian females, most frequently the distal cervical and vertical petrous internal carotid arteries, V3 segments of the vertebral arteries, and the renal arteries (Mettinger and Ericson 1982). Fibromuscular dysplasia may lead to arterial dissection, aneurysm or fistula formation, thromboembolic phenomena, and hemodynamic failure in the affected arterial territory (Piechowski-Jozwiak and Bogousslavsky 2004). The pathologic process results in rings of fibrous tissue and smooth muscle segments, producing the classical "string of beads" appearance on angiogram and arterial dissections and, less commonly, tubular stenosis and fusiform dilation (Funke and Tien 1994). Stroke can result from dissection as well as progressive arterial occlusion. In the Lausanne Stroke Registry, fibromuscular dysplasia accounted for 4% of strokes in patients 16 to 30 years old and 1% of strokes in patients 31 to 45 years (Bogousslavsky and Pierre 1992).

Cervical arterial dissection accounts for 10% to 20% of ischemic strokes in young adults (Schievink 2001). Dissection may occur spontaneously or follow mild or severe trauma, chiropractic manipulation, surgical procedures, sudden head version, or neck hyperextension (Schievink 2001; Schwartz et al 2009). An underlying connective tissue disorder has been postulated in some cases (Brandt et al 2001). Dissection is associated with fibromuscular dysplasia, Marfan syndrome, Ehlers-Danos syndrome type IV (North et al 1995; Schievink 2004), cystic medial necrosis, osteogenesis imperfecta, pseudoaneurysm elasticum, autosomal dominant polycystic kidney disease, alpha1-antitrypsin deficiency, redundancy of the internal carotid artery, lentiginosis, and infection (Rubinstein et al 2005; Schwartz et al 2009). A multicenter observational study assessed the relationship between the subtypes of migraine and cervical artery dissection (carotid or vertebral artery) in younger patients with stroke. Migraine--particularly without aura--was more frequent in patients with cervical artery dissection presenting with ischemic stroke (35%) than in patients with cerebral infarct not due to cervical artery dissection (27%). Both groups of patients had mild strokes (mean NIHSS score of 6; mean age of 44 years). The pathophysiology and causative relationship between migraine and cervical artery dissection remains to be fully understood (Metso et al 2012).

The gold standard diagnostic modality remains cerebral angiography. Less invasive alternatives include CTA and MRI/MRA. CTA may demonstrate a filling defect suggestive of thrombus or intimal flap. A T1-fat-suppressed sequence should be requested on MRI to assess for extraluminal T1-hyperintense material suggestive of methemoglobin in the dissection flap. Level I evidence has not yet proven the sensitivity or specificity for these techniques. The overall prognosis for carotid dissections is better than
that of vertebral dissections. In 1 group of patients, 76% of carotid dissections completely recovered neurologic function (Mokri et al 1986; Mokri et al 1988), and less than 5% suffered fatal stroke or hemorrhage. Ten percent of patients with vertebral artery dissection die in the acute phase secondary to massive stroke or intracranial extension. The latter is usually associated with a dissecting pseudoaneurysm and has a worse prognosis than extracranial dissection (Hart and Easton 1985; Blunt and Galton 1997) due to a fulminant presentation with posterior fossa subarachnoid hemorrhage and a high rate of rebleeding. Pseudoaneurysm formation was more frequent in internal carotid dissections (22%) than in the vertebral artery (14%) in a series of 177 cervical artery dissection patients with a mean age of 44 (Schwartz et al 2009). With the exception of dissecting vertebral-basilar pseudoaneurysms, recurrent dissection is rare: less than 2% in studies from academic centers and even lower in epidemiological studies (Lee et al 2006; Schwartz et al 2009).

Moyamoya disease is a noninflammatory vasculopathy most prominent in Asia (annual incidence is 0.35 per 100,000 Japanese inhabitants) (Kuroda and Houkin 2008) that usually affects children older than 6 years of age. Ratio of females to males affected is 1.8 to 1. Moyamoya disease is characterized by initially asymmetric, progressive, steno-occlusion of both supraclinoid internal carotid arteries and the circle of Willis that may result in recurrent ischemic or hemorrhagic strokes or seizures. Ischemic infarcts are more common in children; hemorrhagic infarcts are more common in patients older than 30 years of age (Love and Biller 2009). Six angiographic stages are described: stage I consists of supraclinoid internal carotid artery stenosis; stages II through V consist of progressive appearance then disappearance of moyamoya vessels; and stage VI consists of external carotid artery branches supplying the intracranial circulation due to occlusion of the major intracranial vessels (Suzuki and Kodama 1983). The posterior cerebral arteries are spared until late in the disease. The classic angiographic appearance is a faint blush of contrast akin to “a puff of smoke” secondary to the development of multiple, fragile collateral vessels in the basal ganglia and thalami that are prone to hemorrhage. Two additional subtypes of moyamoya may manifest late in the disease: ethmoidal (Suzuki and Kodama 1971) and vault (Kodama et al 1980). The former is primarily supplied by the ophthalmic artery and posterior and anterior ethmoidal arteries. The latter is supplied by transdural anastomoses from the middle meningeal or superficial temporal arteries. Moyamoya disease is associated with a number of systemic conditions, including sickle cell disease, Down syndrome, neurofibromatosis type I, radiation therapy, neonatal anoxia, coarctation of the aorta, and certain infections such as tuberculosis (Yamashiro et al 1984; Yilmaz et al 2001). Surgical revascularization procedures include superficial temporal artery-middle cerebral artery (STA-MCA) bypass or rarely, superficial temporal artery-anterior cerebral artery (STA-ACA) bypass, occipital artery-middle cerebral artery (OA-MCA) bypass, encephaloduroarteriosynangiosis (EDAS), or encephaloduroarteriomyosynangiosis (EDAMS) (Yilmaz et al 2001; Kuroda and Houkin 2008).

Stroke from reversible cerebral arterial vasoconstriction or Call-Fleming syndrome, is gaining recognition (Singhal et al 2002; Singhal 2004a; Singhal 2004b; Calabrese et al 2007). It has been described in a variety of conditions, including pregnancy and the puerperium (postpartum angiopathy), migraine, use of vasoconstrictive drugs, reversible posterior leukoencephalopathy, blood transfusions, tumors (eg, phaeochromocytoma), medical conditions (hemolysis, antiphospholipid syndrome, thrombotic thrombocytopenic purpura), and benign angiopathy of the central nervous system (Miller et al 2015). In a retrospective analysis of 139 patients at 2 academic centers that included cases of “probable” reversible arterial vasoconstriction syndrome, the patients were predominantly female (80%) and had a mean age of 42 (Singhal et al 2011). One-third of these patients had a history of vasoconstrictive drug exposure and 6% were recent postpartum patients. Forty-three percent of patients had focal neurologic deficits. Brain ischemia (often watershed rather than territorial infarcts) was documented in around 40% of patients. Subarachnoid hemorrhage overlying the hemispheric convexity was found in 34%; and 20% of patients had lobar hemorrhage. Arterial narrowing (most often by transfemoral or CT angiography) was severe in nearly all patients, even in the absence of cerebral lesions on brain imaging, and complete resolution of the stenosis in the angiographic follow-up occurred in around 70% of patients. A good outcome was observed in 90% of patients, and only 2% of patients died. Out of 159 patients aged 18 to 45 years who were admitted in a stroke unit with acute cerebral infarct found on brain MRI, 21 patients (13%) had multifocal segmental stenosis (mean of 4.52 per patient) in at least 2 different intracranial arteries on 3D-TOF-MRA or CTA performed on the day of admission, and ended up with proven spontaneous reversibility of all segmental stenosis within 3 to 6 months. This finding was the only abnormality observed, despite an extensive etiological investigation, and was considered by the authors to be a variant of a reversible vasoconstriction syndrome (Wolff et al 2015). These patients had a number of differences compared with others reported in large series of reversible arterial vasoconstriction syndrome: they were younger (mean age of 32) and predominantly male; they showed a higher frequency of traditional stroke risk factors; 74% of them had unusually severe headaches during a...
mean of 9 days before the onset of stroke; and none of them had the classically recurrent thunderclap headache. A precipitating factor (mostly cannabis use) was identified in 81% of these patients and cerebral infarcts were found in all of them on neuroimaging studies, with territorial infarcts predominating in the posterior circulation. At 3 months all patients showed a good outcome (Wolff et al 2015).

Misdiagnosis is common because clinical and radiological features may overlap with primary cerebral vasculitis. The preeminent factors for distinguishing between reversible cerebral vasoconstriction syndrome and primary angitis of the central nervous system can be an explosive onset or worst-ever headache with recurrent thunderclap headaches in the next few days, the clinical setting, the type and location of brain lesions, and normal cerebrospinal fluid results (Singhal et al 2011).

Common causes of cardiac emboli in the young include prosthetic heart valves, rheumatic valvular disease, bacterial endocarditis, atrial septal aneurysm, patent foramen ovale, dilated cardiomyopathy, ischemic dyskinetic segments, atrial myxomas, and mitral valve prolapse. Less common sources of cardiac emboli are nonbacterial thrombotic (marantic) and Libman-Sacks endocarditis. Marantic endocarditis is characterized by multiple, sterile, fibrin or platelet thrombi adherent to the mitral and aortic valves, usually in patients with mucin-secreting malignancies. Libman-Sacks endocarditis occurs in patients with systemic lupus erythematosus and is characterized by verrucous, fibrinous lesions of the mitral and aortic valves, leading to valvular insufficiency.

Rheumatic fever remains the most common cause worldwide of acquired heart conditions in the young and an eminently preventable etiology of stroke. The mitral valve is most frequently affected, followed by the aortic valve. The lifetime risk of embolism with rheumatic mitral stenosis is 20%; cerebral embolism is present in 60% of these cases and is more likely if atrial fibrillation, left atrial enlargement, low cardiac output, or severe mitral stenosis is present (Biller et al 2009). Rheumatic fever should be suspected with clinical manifestations such as fever, arthralgia or arthritis, pains, subcutaneous nodules, chorea, or erythema marginatum following tonsillitis/arthritits. Pharyngeal cultures growing beta-hemolytic streptococcus or serum streptococcal antibody titers are diagnostic. Less commonly, ischemic stroke may be associated with the tetralogy of Fallot, Eisenmenger complex, patent ductus arteriosus, or other cardiac valvular abnormalities. The prevalence of cardiac abnormalities in the asymptomatic population must be considered when attributing cause to stroke in a younger population. This is particularly true for a high-prevalence condition such as mitral valve prolapse, which may be no more common in stroke patients (2.7%) than in controls (2.7%) (Gilon et al 1999). One referral center study reported a 24% to 29% proportion of ischemic strokes attributed to cardiac embolism (Adams et al 1986). A population-based study reported a 28% to 31% proportion of ischemic strokes attributed to cardiac embolism (Hart and Miller 1983). The variability in estimates (from 10% to 40%) may be due to extent of cardiac evaluation. Transesophageal echocardiography may be superior to transthoracic echocardiography for the detection of a cardiac source of cerebral embolism (Mas et al 2001; Musolino et al 2003) due to improved visualization of left atrial appendage thrombi, valvular vegetations, atrial septal aneurysms, and patent foramen ovale with the latter. The addition of Doppler color flow studies is especially useful to assess structural features and flow characteristics of prosthetic heart valves.

Paradoxical embolization is a presumed cause of so-called cryptogenic stroke in the young. Patent foramen ovale is more frequently found in patients with cryptogenic stroke than in those with known etiology or in healthy control patients. A thorough work-up should be undertaken to identify a venous source of emboli to traverse the shunt; if absent, the presence of a patent foramen ovale should only be considered a possible cause for the stroke (Cramer et al 2004). Patients with both a patent foramen ovale and atrial septal aneurysm have a much higher stroke risk than patients with either 1 of these conditions (OR 23.93; 95% CI: 3.09-185.42) (Mas et al 2001; Piechowski-Jozwiak and Bogousslavsky 2013). Spontaneous echo contrast is found in up to 9% of transesophageal echocardiograms in young stroke patients (DiTullio et al 1993). Although its significance is unclear, it is caused by sluggish left atrial blood flow and is more common in atrial fibrillation.

Characteristics of cardioembolic stroke include abrupt onset of neurologic deficit maximal at onset that is often triggered by activity. Association with Valsalva maneuver or acute pulmonary hypertension may also suggest paradoxical embolism (Biller et al 2009). Prior transient ischemic attacks in the same arterial territory are unlikely. A good history should evaluate for episodic palpitations, lightheadedness, or a history of sick sinus syndrome or atrial fibrillation (Cohen et al 1993). Although nearly half of cardioembolic strokes are related to atrial fibrillation, the latter is found in only 0.4% of adults younger than 60 years of age (Biller et al 2009). In the last few months, after prolonged cardiac monitoring, the prevalence of previous or de novo atrial fibrillation was found to be 9% (14 patients, 8 with
paroxysmal atrial fibrillation and 5 with permanent atrial fibrillation) among 157 young adults with brain infarction (mean age of 43, 60% males). In this series, atrial fibrillation was more commonly associated with valvulopathy or cardiomyopathy (Prefasi et al 2013). In another study that included long-term ECG Holter monitoring performed after a median of 39 days from admission for the index event, a 10% rate of atrial fibrillation was found in 98 patients aged 18 to 49 with acute cerebral infarct. The mean time from start of long-term ECG Holter monitoring to detection of arrhythmia (mainly in paroxysmal form) was 11.5 days. In contrast to Prefasi's series, structural heart disease was found in only 10% of the atrial fibrillation patients. These patients had an elevated level of acute serum cardiac markers (N-terminal probrain natriuretic peptide and high sensitive troponin T). N-terminal probrain natriuretic peptide may be a predictor of atrial fibrillation (Sanak et al 2015).

Table 2. Conditions Associated with Cardiac Emboli

**Probable source**
- Endocarditis
- Atrial fibrillation
- Recent myocardial infarction
- Akinetic segment
- Dilated cardiomyopathy
- Intracardiac thrombus
- Cardiac tumors
  - Atrial myxoma
  - Cardiac rhabdomyoma
  - Cardiac papillary fibroelastoma
- Sick sinus syndrome
- Valvular vegetations including nonbacterial thrombotic endocarditis
  - Nonbacterial thrombotic endocarditis
  - Libman-Sacks endocarditis
- Rheumatic valvular disease
- Prosthetic valve
- Right-to-left shunt with associated venous thrombosis
- Spontaneous atrial contrast echo
- Atrial septal aneurysm
- Intracardiac tumors
- Recent cardiac procedures
  - Bypass graft
  - Valvular surgery
  - Heart transplantation
  - Extracorporeal membrane oxygenation (ECMO)

**Possible source**
- Mitral valve prolapse
- Atrial flutter
- Remote myocardial infarction
- Left ventricular hypertrophy
- Hypokinetic segment
- Atrial septal aneurysm
- Isolated atrial septal defect or patent foramen ovale (without associated venous thrombosis)
  - Mitral annular calcification
  - Calcific aortic stenosis
  - Coarctation of the aorta
  - Mitral valve strands
  - Aneurysm of the sinus of Valsalva
  - Left ventricular aneurysm

Adapted from (Stern and Wityk 1994).

The spectrum of hematologic causes of stroke includes primary hypercoagulable syndromes and secondary
hypercoagulable states. Primary hypercoagulable states are caused by quantitative or qualitative abnormalities of specific coagulation proteins leading to a lifelong predisposition to thrombosis. Secondary hypercoagulable states, a diverse group of mostly acquired conditions, cause a prothrombotic state by complex mechanisms (Nachman and Silverstein 1993). Ischemic stroke can be the presenting feature of a hematologic disorder (Table 3). A hypercoagulable state accounts for 1% to 2% of all stroke and 2% to 7% of stroke in patients younger than 50 years. The inherited thrombophilias (ie, protein C, S, and antithrombin deficiencies) are relatively common at 1:200 to 1:2000 in the heterozygous form, but the frequency of symptomatic deficiency is only 1:36000 (Greaves 1993; Martin et al 1997). Symptomatic episodes are usually venous thromboses; hereditary deficiencies of proteins C, S, or antithrombin III are rare in ischemic stroke patients younger than 45 years (Douay et al 1998). Resistance to activated protein C due to a mutation in factor V (factor V Leiden) and a mutation in the prothrombin gene (20210A) have been shown to be important genetic risk factors for venous thromboembolic disease, including cerebral venous thrombosis (Martinelli et al 1998), but less likely for arterial ischemic stroke (Zunker et al 2001). One study determined the odds ratio for carriers of factor V Leiden mutation compared to noncarriers to be 2.56. Relationship with the factor V Leiden mutation was greater in women (odds ratio 3.95), and the combined presence of factor V Leiden mutation plus at least 1 vascular risk factor increased the odds ratio to 10.72 (Margaglione et al 1999). An important note is that acute thrombosis itself may cause transient decreases in proteins C, S, and antithrombin. The acute evaluation for these deficiencies, therefore, may yield inaccurate results. Also, heparin has been found to lower antithrombin levels, and warfarin lowers functional levels of protein C and S. Conditions with hematologic changes possibly leading to stroke include pregnancy, cancer, nephrotic syndrome, leukemia, inflammatory bowel disease, acute infection, paroxysmal nocturnal hemoglobinuria, and Behçet syndrome. Finally, antiphospholipid antibodies have been associated with ischemic stroke in some studies; however, their causative role in stroke is not entirely clear (Brey et al 2002). To estimate the frequency of any antiphospholipid antibodies (aPL) in patients with stroke between 16 and 50 years of age (median age of 37), Sciascia and coworkers identified 5217 patients (3349 stroke patients and 1868 controls) included in 43 studies (6 prospective studies with 408 patients) in a systematic review of available relevant papers in electronic databases from 1970 to 2013 (Sciascia et al 2015). In young stroke patients, the frequency of any antiphospholipid antibody was 17%; anticardiolipin antibodies (aCL), lupus anticoagulant, and anti-β2 glycoprotein 1 antibodies were found in 22%, 16%, and 14% of these patients, respectively. Despite significant heterogeneity and methodological flaws observed in the studies included, the authors maintain that the results suggest a robust association between antiphospholipid antibody and stroke when compared with young control individuals. Accordingly, an antiphospholipid antibody positivity test may be associated with a 5-fold higher risk for cerebrovascular event (ischemic stroke or transient ischemic attack). A hypercoagulable screen is warranted when venous thrombosis with paradoxical embolism is suspected, when there is a family history of recurrent thrombosis, or when there is a personal or family history of recurrent miscarriage.

Table 3. Selected Hematologic Disorders Associated with Stroke
- Sickle cell disease
- Hemoglobin SC disease
- Polycythemia
- Hyperviscosity state
- Thrombocytosis
- Heparin-induced thrombocytopenia
- Iron deficiency anemia
- Thrombotic thrombocytopenic purpura
- Paroxysmal nocturnal hemoglobinuria
- Hyperhomocysteinemia and homocystinuria
- Disseminated intravascular coagulation
- Antiphospholipid antibodies
  - Lupus anticoagulant
  - Anticardiolipin antibodies
- Antithrombin deficiency
- Protein C deficiency
- (Free) Protein S deficiency
- Activated protein C resistance (including, but not limited to, Factor V Leiden mutation)
- Disorders of fibrinolysis
- Methylene tetrahydrofolate reductase (MTHFR) mutation C677T
- Plasminogen activator promoter polymorphism (PAI-1)
- Prothrombin gene 20210A mutation

Adapted from (Stern and Wityk 1994).

Multiple drugs, illicit and otherwise, have been associated with stroke, including over-the-counter sympathomimetics such as phenylpropanolamine, ephedrine and pseudoephedrine, amphetamines, alcohol, heroin, cocaine, phencyclidine, lysergic acid diethylamide, marijuana, and more recently, synthetic cannabinoids (“spice”) (Kernan et al 2000; Wolff and Jouanjus 2017). Up to 14% of ischemic and hemorrhagic infarcts in individuals aged 18 to 44 years were caused by substance abuse in a study (Westover 2007). Patients may not provide an accurate history regarding substance abuse; therefore, a complete physical examination, including skin exam for presence of needle marks, should raise suspicion for drug abuse. Blood and urine toxicology should also be obtained. The possibility of septic endocarditis should also be considered in the intravenous drug abuser. Based on a valid and reliable inpatient-care database from a United States data source, recreational marijuana use was found to be independently associated with ischemic stroke in a retrospective analysis (from 2004 to 2011) of patients aged 15 to 54 years (Rumalla et al 2016). Compared with non-users, recreational marijuana users had a 17% higher probability of hospitalization due to acute cerebral infarction in all stratified age groups of individuals between 15 and 54 years. This probability was even higher when marijuana use was combined with tobacco use (31%) or cocaine use (42%).

Stroke is a rare complication of migraine (Tzourio et al 1995; Chang et al 1999). The overall incidence of migraine-associated stroke is 3.36 per 100,000 per year. In individuals without other stroke risk factors, the incidence decreases to 1.44 per 100,000 per year. Migraine with aura and the subtypes of migraine, such as familial hemiplegic migraine, and basilar, retinal, and ophthalmoplegic migraine have a higher stroke risk. Several case-control studies have demonstrated an approximately 4-fold higher stroke risk in women with migraine under age 45 years; within this population, the risk increases to 10-fold in smokers and 14-fold in those taking oral contraceptive pills. The risk is highest (odds ratio of 34) in young women with migraine who smoke and take oral contraceptive pills. This association is inconsistent in older women and men. Given the high prevalence and incidence rates of migraine (10% to 25%) and ischemic stroke and the high prevalence of headache in patients with stroke, it is important to distinguish between (1) stroke of another cause coexisting with migraine, (2) stroke of another cause (eg, carotid artery dissection) presenting with clinical features of migraine with aura, and (3) stroke occurring during the course of a typical attack of migraine with aura (Welch 1994). The aura of migraine is a key risk factor for cerebral ischemia. Stang and colleagues found that migraine with aura was strongly associated with verified stroke (O.R. 2.81) as well as symptoms of stroke (O.R. 5.46) and symptoms of TIA (OR 4.28); the association was not significant in patients with headache without aura (Stang et al 2005). In the last few months, a large population-based study of Asian patients has come to light that assessed the incidence of ischemic stroke in a neurologist-diagnosed migraine cohort of 119,017 patients aged over...
20 years and a nonheadache-matched comparison cohort (119,017 individuals) (Peng et al 2016). After a mean follow-up of 3.6 years, the migraine-cohort patients showed a risk of ischemic stroke 1.24 times higher than the comparison-cohort individuals. Moreover, in female aural migraine patients younger than 45, the risk of cerebral infarct was 6 times higher.

The mechanisms underlying the relationship between migraine and cerebral ischemia are not yet well understood. Migraine-specific mechanisms, potential common biological mechanisms (endothelial dysfunction, patent foramen ovale, and hypercoagulability), atherosclerotic mediated mechanisms, and genetic influence—likely all acting synergistically—might be operating to increase the propensity of cerebral ischemia in migraine (Pezzini et al 2011). Young age, female sex, a history of “high-risk” migraine subtypes (eg, familial hemiplegic migraine), cigarette smoking, use of oral contraceptives, onset with typical but perhaps more severe migrainous headache, prolonged aura, spreading or marching symptoms, visual and cortical symptoms, and posterior circulation infarct on brain imaging are factors that raise suspicion for migrainous stroke. Criteria for the diagnosis of migraine-induced stroke include: (1) previously established diagnosis of migraine with aura, (2) onset of infarction occurring during the course of a typical migraine aura attack, (3) persistent aura symptoms for more than 60 minutes, (4) evidence of ischemic infarction in relevant location by neuroimaging, and (5) no other obvious cause of infarction (Headache Classification Committee of the International Headache Society 2013).

Migrainous infarction accounts for 13.7% of ischemia in young adults (Arboix 2003). Migraine-associated acute cerebral ischemia was identified in 17 individuals (11 having migraine with aura) in a prospectively collected data set of 8137 stroke patients over an 11-year period, amounting to an estimated frequency of around 2 cases per 1000 strokes per year (Wolf et al 2011). These patients were younger women with a longstanding (mean of 13 years) history of migraine and prolonged aura symptoms. Moreover, a high prevalence of patent foramen ovale was identified and lesions were small, most often involving the posterior circulation. The overall outcome was favorable (Wolf et al 2011). Therefore, migrainous infarction is a diagnosis of exclusion. Because migraine is a clinical diagnosis without a diagnostic marker or unique radiographic features, alternative etiologies such as arteriovenous malformation, cervical arterial dissection, antiphospholipid syndrome, MELAS, or cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) should be pursued if the presentation is not highly consistent.

Infection (particularly chlamydia and HIV) and acute and chronic inflammation have been attributed to raising stroke risk in younger patients (Bova et al 1996; Macko et al 1996; Pinto 1996; Qureshi et al 1997; Madre et al 2002; Anzini et al 2004; Cole et al 2004). A population-based study found AIDS to be a major risk factor for ischemic as well as hemorrhagic stroke (Cole et al 2004). In a nationwide population-based cohort study, HIV-infected individuals had an increased risk of stroke compared to their controls (Rasmussen et al 2011). The relative risk was substantially higher in the injection-drug-abuse HIV-infected individuals (35.6 median years), particularly for intracerebral and subarachnoid hemorrhage. High stroke risk was further associated with low CD4 cell count before the start of HAART, and also with abacavir treatment, although not with HAART, in general. Diagnostic considerations in the infection setting include meningovascular syphilis; nonbacterial thrombotic endocarditis with cardiogenic embolism; vasculopathies associated with cryptococcal, tuberculous, and lymphomatous meningitis; toxoplasmosis; and herpes zoster.

Stroke can result from inherited disorders such as MELAS and CADASIL. MELAS is a disorder of mitochondrial metabolism resulting from a point mutation in mitochondrial DNA encoded transfer RNA for leucine. The pathology of stroke remains unclear. Patients typically present with ischemic-appearing lesions that are not restricted to a single arterial vascular territory, migraine-like headaches, seizures, emesis, and lactic acidosis and may have myopathy, ataxia, cardiomyopathy, diabetes, retinitis pigmentosa, or renal abnormalities. Muscle biopsy reveals ragged red fibers. Patients with CADASIL typically present with recurrent subcortical strokes (Joutel et al 1996; Markus et al 2002). Specific mutations in the notch 3 gene on chromosome 19 have been identified in patients with CADASIL. Brain MRI typically reveals a diffuse leukoencephalopathy with infarcts in the basal ganglia and white matter bilaterally, extending into the anterior temporal lobes and external capsules. Cerebral microhemorrhages are common (Viswanathan and Chabriat 2006). Imaging abnormalities can precede stroke-like symptoms by several years. Diagnosis is made by skin biopsy. Another condition associated with stroke is Hashimoto encephalopathy with cerebral vasculitis. Clinical presentation includes relapsing and remitting neurologic symptoms and signs of seizures, myoclonus, stroke-like episodes, cognitive decline, and neuropsychiatric manifestations (Mocellin 2007). Some migraine patients may present with headache, reversible neurologic deficits, and recurrent cerebrospinal fluid lymphocytosis (HaNDL) syndrome; their neuroimaging studies are normal (Fumal et al 2005).
**Fabry disease**, or **Anderson-Fabry disease**, is an X-linked recessive lysosomal storage disorder due to alpha-galactosidase-A deficiency (mutation of the gene at Xq22.1) leading to a glycosphingolipid accumulation in neurons and vascular endothelial and smooth muscle cells. Men and women are similarly affected, with a wide range of clinical manifestations from asymptomatic states to irreversible organ failure.

Fabry disease affects the peripheral and central nervous systems, as well as the myocardium, kidney, and the gastrointestinal system. Nonneurologic clinical manifestations on the skin (angiokeratoma corporis diffusum), corneal opacity (cornea verticillata), subcapsular cataracts, hypohidrosis, and acroparesthesias often develop in childhood or adolescence, although they may occasionally be absent in young adults, making the diagnosis of Fabry disease a challenge. Stroke is the leading complication of Fabry disease in the central nervous system. The leading complication of Fabry disease is stroke (Shi et al 2014). Cerebral infarcts and transient ischemic attacks are the most prevalent stroke subtypes, sometimes presenting as the first manifestation of this disease, thus, leading to its diagnosis. Large vessel and small vessel symptomatic infarcts are most common, although chronic white matter hyperintensities, usually asymptomatic, may also be found on neuroimaging studies. Intracerebral or subarachnoid hemorrhages, microbleeds, and **cerebral venous thrombosis** are less common occurrences in Fabry disease (Kolodny et al 2015).

Fabry disease is considered an uncommon, though treatable, cause of stroke. The stroke pathogenesis associated with Fabry disease is incompletely understood, despite its association with arterial ectasia, endothelial dysfunction, premature atherosclerosis, and cardiopathy (hypertrophic and restrictive cardiomyopathies, valvular and conduction-system abnormalities). In a metaanalysis of 9 studies (8 ranked moderate to high quality by a designed assessment tool; 4 studies focusing on cryptogenic stroke and the remainder on all stroke etiologies) comprising around 8000 patients with a mean age range between 38 to 51 years, the prevalence of Fabry disease was higher in patients with cryptogenic stroke (0.6% to 11%), whereas it ranged from 0.4% to 2.6% in stroke of any etiology. A male predominance in the prevalence of Fabry disease was observed in cryptogenic stroke (4.5% vs. 3.4% in women), but no gender difference in the prevalence of Fabry disease was observed when stroke of any etiology was considered.

Moreover, the incidence of definite or probable Fabry disease was estimated in a prospective multicenter observational study (47 centers in 15 European countries) that included 5023 patients from 18 to 55 years of age (median age of 46) presenting a recent cerebrovascular event (within 3 months; brain infarct in 71% of patients; transient ischemic attack in 22%; **intracerebral hemorrhage** in 5%) (Rolfs et al 2013). In this largest cohort of young stroke patients, Fabry disease was present in 1% (0.5% definite and 0.4% probable diagnosis). Females, younger patients, and ischemic stroke predominated in both diagnostic categories. Territory infarcts were found in 40% and 33% of definite and probable Fabry disease patients, respectively. Interestingly, no association was found between Fabry disease with cardiopathy (congestive heart failure or arrhythmia), and family history of cardiac, renal, or cerebrovascular disease (Rolfs et al 2013).

Many other disorders have been associated with cerebral infarction in the young. Some possible entities are listed in Table 4.

### Table 4. Other Conditions Associated with Stroke

**Inflammatory diseases:**
- Rheumatoid arthritis
- Systemic lupus erythematosus
- Scleroderma
- Sjögren syndrome
- Polymyositis
- Proximal myotonic myopathy
- Henoch-Schönlein purpura
- **Polyarteritis nodosa**
- Churg-Strauss syndrome
- Wegener granulomatosis
- Lymphomatoid granulomatosis
- Sarcoidosis
- Primary vasculitis of the central nervous system
- Behçet disease

**Infectious diseases:**
• Neuroborreliosis
• Neurocysticercosis
• Varicella zoster
• HIV
• Bacterial (pyogenic) meningitis
• Chlamydia pneumonia
• Hepatitis C virus and mixed cryoglobulinemia
• Hydatid cyst embolism
• Leptospirosis

Cancer:
• Tumor emboli
• Malignant angioendotheliomatosis

Hereditary disorders:
• Neurofibromatosis
• Epidermal nevus syndrome
• CADASIL
• Sneddon syndrome
• Williams syndrome

Medication-related:
• Ovarian hyperstimulation syndrome or high-dose female sex hormone therapy
• L-asparaginase
• High-dose intravenous immunoglobulin
• Methotrexate
• Interferons

Other:
• Fibrocartilaginous embolism
• Childhood cerebral arteriopathies
• Dysplastic arteriopathies/arterial abnormalities (PHACES syndrome, Alagille syndrome, Williams Syndrome, Noonan syndrome, and trisomy 21)
• Hashimoto encephalopathy with vasculitis
• Headache, neurologic deficits, and cerebrospinal fluid lymphocytosis (HaNDL) syndrome

Adapted from (Stern and Wityk 1994).

The majority of intraparenchymal hemorrhages are lobar; they may also occur in deep subcortical structures (basal ganglia, internal capsule), brainstem, or cerebellum, depending on etiology (Del Brutto et al 1999; Ruiz-Sandoval et al 1999). In a study of intracerebral hemorrhage in young adults, ruptured arteriovenous malformations were found in 29%; hypertension in 15%; ruptured aneurysms in 10%; miscellaneous conditions in 22%; and undetermined causes in 24% (Toffol et al 1987). Another study of intracerebral hemorrhage in young people noted vascular malformations in 49% of patients; hypertension in 11%; cerebral venous thrombosis in 5%; sympathomimetic drug use in 4%; toxemia of pregnancy in 4%; and cryptogenic cause in 15% (Ruiz-Sandoval et al 1999). Excluded from this study were primary subarachnoid hemorrhage, trauma, past evidence of vascular malformation, and brain tumor. The importance of repeat vascular imaging (ideally catheter angiography) after an interval of 8 to 12 weeks to allow for resolution of intracranial blood products cannot be overstated as repeat workup of intraparenchymal hemorrhages in young adults without vascular risk factors often yields a previously occult vascular malformation. (embed="pagecomponents/media_embed" entry_id="8686")

Selected causes of hemorrhagic events are listed in Table 5. Normotensive patients with lobar hemorrhages are especially likely to have an underlying vascular lesion (see Vignette 3). Patients with cavernous malformations occasionally have a familial history, as do 20% to 30% of individuals with an aneurysm (Gunel et al 1996). Familial aneurysms are more common in women below the age of 50 years (Leblanc 1996). Disorders associated with intracranial saccular aneurysms include autosomal dominant polycystic renal disease, pseudoaxanthoma elasticum, Ehlers-Danlos type IV, Marfan syndrome (possibly), neurofibromatosis, coarctation of the aorta, arteriovenous malformations, and moyamoya disease. Mycotic aneurysms represent 4% of all intracranial aneurysms and occur in
3% of patients with infective endocarditis (Frazee et al 1980). They may be saccular or fusiform and frequently occur in distal branches of the middle and posterior more than anterior cerebral arteries. Due to the peripheral location, mycotic aneurysm rupture frequently results in intraparenchymal, not subarachnoid, hemorrhage.

**Table 5. Selected Causes of Spontaneous Intracranial Hemorrhage**

- Trauma
- Aneurysm
  - Berry
  - Mycotic
  - Dissecting pseudoaneurysm
- Vascular malformation
  - Arteriovenous malformation (AVM)
  - Dural arteriovenous fistula (dAVF)
  - Cavernous malformation
- Hypertension
- Coagulopathy
- Arteritis
  - sterile
  - infectious
- Sympathomimetic drugs
  - cocaine and crack cocaine
  - fenfluramine and phentermine
  - phenylpropanolamine, ephedrine/ephestra
- Hemorrhage into a tumor
- Moyamoya disease or syndrome
- Hereditary intracerebral hemorrhage
  - Dutch type (mutation in amyloid precursor protein gene)
  - Icelandic type (mutation in cystatin C)

Adapted from (Stern and Wityk 1994).

Unfortunately, even after an exhaustive evaluation for etiology of stroke in the younger patient, up to 40% of cases remain without a known etiology. In a survey of ischemic stroke in the young, 44% of patients had known cause of stroke, although 1 in 5 of these patients may have been inadequately investigated, resulting in a spuriously high percentage of cryptogenic cases (Chan et al 2000). A complete diagnostic evaluation is, therefore, critical in order to determine potential causes and effective secondary stroke-prevention strategies.

**Diagnostic workup**

A careful patient history, physical examination, and laboratory evaluation, as well as specific diagnostic techniques in appropriate patients can elucidate many etiologies of stroke in this group of patients. The history can provide clues to the cause of the stroke. A history of deep venous thrombosis or miscarriage may alert the physician to an occult coagulation abnormality. Repeated questioning of patients and family members regarding possible illicit drug use may clarify this issue. Subtle head trauma or rapid or prolonged head and neck extension may be helpful historical points. A family history of headache or early onset stroke may be relevant as well. The physical examination should include a careful evaluation of the cardiovascular system and skin, a formal ophthalmologic evaluation (Table 6), and a complete neurologic assessment.

**Table 6. Clues from Examination of the Eyes and Skin**

<table>
<thead>
<tr>
<th>Examination Finding</th>
<th>Possible cause</th>
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An organized and stepwise evaluation should follow as needed regarding ancillary testing. Complete blood count with differential, erythrocyte sedimentation rate, electrolytes, glucose, coagulation panel, platelet count, liver and renal function tests, lipid panel, and pregnancy test (if appropriate) are routinely performed (Singhal et al 2013). Specialized investigations to rule out specific etiologies in young adults with stroke may involve toxicological, rheumatological, infectious, hematological, and hypercoagulable panel tests, CSF examination, advanced brain-imaging techniques, brain and leptomeningeal biopsy, and genetic tests (Singhal et al 2013).

Neuroimaging with a CT or MRI (preferred) of the head can confirm the diagnosis and differentiate between an ischemic stroke and a hemorrhagic event. A carotid ultrasound can evaluate for high-grade stenosis of a symptomatic vessel, whereas transcranial Doppler, CT angiography, or MR angiography may be useful to evaluate the intracranial
vasculature for stenosis or collateral flow. Transcranial Doppler sonography can increase the detection of right-to-left intracardiac shunts. Cerebral angiography remains the most sensitive method of vascular imaging and is particularly useful when a dynamic evaluation of the intracranial circulation is required (e.g., hemodynamically significant stenosis, leptomeningeal collateral supply, venous hypertension, or early venous drainage from a vascular malformation). Further evaluation should be performed as indicated, based on the suspected stroke etiology. A cerebrospinal fluid sample should be obtained when vasculitis is suspected or when the history is concerning for subarachnoid hemorrhage and the CT is unrevealing. CT and MR venography (CTV and MRV) are useful for evaluating cerebral venous thrombosis, particularly when a sinus is involved. If cortical venous thrombosis is strongly suspected, despite a negative head CTV/MRV, a diagnostic cerebral angiogram should be performed. When a cardiac embolus is the suspected etiology of cerebral infarction in a young adult, echocardiography should be the primary form of cardiac imaging. Echocardiographic techniques may be helpful to rule out a cardiac source of embolism and may also influence future secondary stroke prevention, depending on high or low risk of cerebral embolism between the different types of cardiopathy. In this setting, transesophageal echocardiography is superior to transthoracic echocardiography for identifying potential cardiac sources of embolism (such as prosthetic valve abnormalities, native valve vegetation, atrial septal anomalies, and thrombus in the left atrium and the left atrial appendage as well as tumors and spontaneous echocardiographic contrast) in young patients with ischemic stroke. Transesophageal echocardiography is a safe, semi-invasive procedure with a low rate of complications, the most serious of which is esophageal perforation (with an incidence of up to 0.09% in all studies performed) (Saric et al 2016).

Transcranial Doppler sonography can increase the detection of right to left intracardiac shunts (Topcuoglu et al 2003). In patients with patent foramen ovale, pelvic MR venography can uncover pelvic vein thrombosis as the source of blood clots (Cramer et al 2004). Cerebral angiography often provides a wealth of information and remains the most sensitive vessel imaging method. Further evaluation should be performed as indicated, based on the suspected stroke etiology. For example, a cerebrospinal fluid sample should be obtained when vasculitis is suspected or when the history is concerning for subarachnoid hemorrhage and the CT is unrevealing.

The diagnostic yield of tests in 215 young adults (mean age of 37) with cerebral infarct involving the anterior (65%) and posterior (30%) circulation has been reported. An extensive diagnostic workup, including prothrombotic and vasculitis panel, toxicology screening, CSF examination, Holter monitoring, echocardiography, and neuroimaging, was performed in almost all patients (Ji et al 2012). Cerebral angiography disclosed an embolic occlusion, severe stenosis, or other vasculopathy, mainly in the proximal segment of the middle cerebral artery, in 64% of the patients. Echocardiography (contrast transthoracic in 91% and transesophageal in 40%) was abnormal in half of the patients; patent foramen ovale was the most common abnormality, affecting 96 patients, and was the only finding in 83 patients; in 76, it was implicated as stroke etiology. Screening for hypercoagulable state gave a diagnostic yield of 16%; functional protein S deficiency and prothrombin 20201 mutation were the most and least commonly observed abnormalities, respectively. Cerebrospinal fluid examination was abnormal in 15% of the patients. A low diagnostic yield (less than 5%) was observed in both toxicological screening and vasculitis panel whereas Holter monitoring had the lowest diagnostic yield (Ji et al 2012).

### Table 7. Ischemic Infarction Diagnostic Testing

#### Laboratory studies
- Complete blood count
- Erythrocyte sedimentation rate
- Chemistry profile
- Fasting glucose, hemoglobin A1C level
- Prothrombin time, activate partial thromboplastin time, platelets
- Toxicology
- Rapid plasma reagin/venereal disease research laboratory
- Fasting lipid profile
- Sickle cell prep
- Blood cultures
- Pregnancy test

#### Brain imaging
• Head CT without contrast
• Head MRI without gadolinium
• High-resolution (3T) contrast enhanced T1-weighted MRI

**Vascular imaging**
• Carotid duplex ultrasound
• Trans/cranial Doppler sonography
• MRA/CTA of head and neck
• Cerebral angiography
• Lower extremity ultrasound, pelvic CT or MR venography (in patients with patent foramen ovale)

**Cardiac studies**
• ECG
• Transesophageal echocardiogram with bubble
• Holter

**Hypercoagulable screen**
• Protein C activity and free protein S antigen
• Antithrombin III
• Activated protein C resistance
• Factor V Leiden mutation
• Russell viper venom time or other screen for lupus anticoagulant and antiphospholipid antibodies (IgG & IgM)/beta2-glycoprotein I antibody
• Thrombin time
• Fibrinogen
• Prothrombin gene 20210A mutation
• MTHFR C677T
• PAI-1

**Other**
• CSF analysis (if vasculitis or infection suspected)
• HIV serology
• ANA
• Lactic acid
• Homocysteine
• ESR
• CRP
• Cryoglobulin level
• Complement levels
• ANCA
• Neutrophil cytoplasm antibody (cANCA and pANCA)
• Scl-70 antibody
• Anti-centromere antibody
• Anti-Ro (SSA) and anti-La (SSB)
• Serum angiotensin-converting enzyme
• Antiproteinase 3
• Lipoprotein (A)
• Brain and meningeal biopsy (suspected vasculitis)
• Skin biopsy
• Sural nerve biopsy
• Muscle biopsy

Adapted from (*Stern and Wityk 1994; Singhal et al 2013*).

**Management**

So far, no evidence-based management guideline for stroke in young adults is available. In general terms, treatment in the acute phase of ischemic stroke is similar in both young and older patients (*Singhal et al 2013*). Even so,
management should be individualized to the patient’s diagnosis. Although the causes of stroke in children differ substantially from that in the adults, the vascular distributions and manifestations of stroke are similar in both groups. General supportive care is an appropriate primary step in treatment. Specific therapy directed at minimizing or treating the offending etiology should be pursued (Ning and Furie 2004). In patients with sickle cell disease between the age of 2 and 16 years, periodic transfusion is recommended in patients with abnormal transcranial Doppler study (Adams et al 1998a; Roach et al 2008). Thrombotic, surgical, antiplatelet, and anticoagulation recommendations are not different from those of most other age groups (Roach et al 2008). To date, thrombolysis is approved for ischemic stroke in patients over 18 years of age. An ongoing trial of thrombolysis in children and adolescents may provide data about the safety and efficacy of thrombolysis in this age group. However, most stroke physicians support the use of intravenous tissue plasminogen activator in carotid dissection and other uncommon etiologies of stroke in young adults (Wagner and Lutsep 2005).

Intravenous alteplase within 4.5 hours of stroke onset was found to be safer and more effective in around 3,250 young stroke patients (18 to 50 years old, median age of 45, median NIHSS score of 10) than in stroke patients 51 to 80 years old (median age of 70, median NIHSS score of 12). The subsets of other and undetermined stroke etiologies according to TOAST criteria were more frequent in young patients than in their older counterparts. Young patients had a better outcome at 3 months (52% with no or minimal disability and 72% with functional independence) than did older patients. Furthermore, symptomatic intracerebral hemorrhage and mortality were lower in younger patients compared to patients over 50 years of age (Toni et al 2012). Intravenous thrombolysis was safe and equally effective in patients aged 18 to 50 years with a cerebral infarct and in ischemic stroke patients aged more than 50 years, according to the results of a retrospective observational study based on a large hospital-based stroke registry (Reuter et al 2015). In this study, 8% of the patients were younger than 50 years of age; a favorable outcome after intravenous thrombolysis (modified Rankin score 1 lower or not worse than pre-stroke mRS) was similar among patients aged 18 to 50 years (OR 1.4) and those aged 51 to 80 years (OR 1.33); patients from 18 to 30 years of age showed the highest benefit from intravenous thrombolysis (OR 2.78). Overall mortality was no different in either group (OR 0.93); nevertheless, in-hospital mortality was lower in patients younger than 50 years of age.

Other therapeutic strategies in hyperacute stroke are being studied. Results of a randomized trial on the intraarterial treatment delivered on top of intravenous thrombolysis in a 6 hour time window in patients with proximal intracranial occlusion in the anterior circulation for the first time proved the efficacy and safety of intraarterial treatment. The studied population included patients from 23 to 96 years of age (mean age 65 years). The interventional arm had better odds for good recovery at 90 days, defined as a modified Rankin scale score of 0 to 2 (OR 1.66; 95% CI: 1.21-2.28). There was no difference in death rates or incidence of any symptomatic intracerebral hemorrhage. There were more ischemic events in other vascular territories though (Berkhemer et al 2015).

Special considerations

Pregnancy

Pregnancy and the postpartum period have long been recognized as important risk factors for both ischemic and hemorrhagic strokes, which occur with similar frequency during this period. Pregnancy increases the risk of stroke by 3-fold to 13-fold; causes of stroke during pregnancy are listed in Table 8 (Dafer and Biller 2009). An important study by James and colleagues reported the incidence of pregnancy-related stroke to be 34.2 per 100,000 deliveries, and the mortality rate to be 1.4 per 100,000 deliveries (James et al 2005). Factors associated with a higher risk for stroke included older age (older than 35 years), African-American race, history of migraine (O.R. 16.9), thrombophilia (O.R. 16.0), SLE (O.R. 15.2), heart disease (O.R. 13.2), sickle cell disease (O.R. 9.1), hypertension (O.R. 6.1), and thrombocytopenia (O.R. 6.0). A higher risk for stroke was found with pregnancy-related complications such as postpartum hemorrhage, preeclampsia, gestational hypertension, need for blood transfusion, postpartum infection, and placental abruption with disseminated intravascular coagulation.

The risk for pregnancy-related stroke is highest in the postpartum period (up to 6 weeks postpartum). Kittner and colleagues found the relative risk for ischemic stroke to be 0.7 during pregnancy; this increased to 8.7 during the postpartum period. The relative risk was found to be 2.5 for intracerebral hemorrhage (exclusive of subarachnoid hemorrhage) but dramatically increased to 28.3 for the postpartum period (Kittner et al 1996). Most arterial strokes occurred in the third trimester and puerperium, whereas all but 1 venous infarct occurred in the puerperium (Jaigobin and Silver 2000). In addition to cerebral venous thrombosis, postpartum angiopathy is an important cause for headache in the postpartum period (Singhal 2004b; Gladstone et al 2005; Singhal and Bernstein 2005). Therefore,
The results of 151 pregnancy-related strokes were reported in a retrospective analysis to evaluate data on stroke during pregnancy, delivery, and puerperium collected over a 2-year period (2012 and 2013) in 736 teaching hospitals in Japan (Yoshida et al 2017). Interestingly, a higher proportion of hemorrhagic stroke occurred in this study than that reported in Western countries. Out of 111 patients, 73% suffered hemorrhagic stroke, 37 women (25%) had an ischemic stroke, and the remainder had a mixed type of stroke (hemorrhage and infarct simultaneously). The mean age of the 111 patients with hemorrhagic stroke was 32 years, and half of the hemorrhages occurred during pregnancy (mean gestational age: 25 weeks); 14% of hemorrhages occurred at delivery (mean delivery weeks: 38.9), and 25% occurred during puerperium (most after 24 hours postpartum). The 4 leading etiologies of hemorrhagic stroke were aneurysm (20%), arteriovenous malformation (19%), pregnancy-induced hypertension (12%), and HELLP syndrome (8%). The cause could not be determined in 16% of patients with hemorrhagic stroke. At discharge, 40% of patients exhibited a modified Rankin scale of at least 3. The in-hospital mortality rate was 11%; poor functional outcome was higher in patients with HELLP syndrome (66%) and pregnancy-induced hypertension (46%), whereas just one third of patients with aneurysms and arteriovenous malformation had a poor functional prognosis (Yoshida et al 2017).

The mean age of the 37 patients with ischemic stroke was 30 years; stroke presentation for 50% of these cases was during pregnancy (mean gestational age: 21 weeks), whereas one third (11 patients) developed ischemic strokes during puerperium (most after 24 hours postpartum), and the remaining 4 cases occurred at delivery (mean delivery weeks: 31.5). Reversible vasoconstriction syndrome was the etiology in approximately 25% of ischemic strokes (9 patients), and coagulopathy was the etiology in 16% (6 patients). Cardiogenic embolism, small-vessel disease, and large-artery atherothrombotic disease each accounted for 5% of ischemic strokes and 9 patients (24%) had a venous infarction. The etiology remained undetermined in 11% of patients. The in-hospital mortality rate was 2.7%, and 83% of surviving patients had a good clinical outcome (Yoshida et al 2017).

In 240 women of Hispanic origin with cerebrovascular complications occurring during pregnancy and in the first 5 weeks after delivery, 56% developed cerebral venous thrombosis (mean age of 23), 27% had cerebral infarction (mean age of 26), and 16% suffered an intracerebral hemorrhage (mean age of 29) (Cantu-Brito et al 2011). Cerebral venous thrombosis and cerebral hemorrhage peaked during the first and third trimester of pregnancy, respectively, and cerebral infarcts also occurred most frequently in the first and third trimester. Preeclampsia and eclampsia were noted in around one-half and one-third of cerebral hemorrhages and infarcts, respectively, whereas frequencies were lower in cerebral venous thrombosis. Outcome was favorable in over one-half of the women with cerebral venous thrombosis and cerebral infarction, but in only one-third of the women with intracerebral hemorrhage.

In a retrospective study of 24 women with a previous ischemic stroke (20 of which were of arterial origin), no recurrence of cerebral infarct was found during pregnancy and puerperium, although 1 woman had a transient ischemic attack at the 35th week of gestation. The main etiologies of previous ischemic stroke were hypercoagulable state (41%) and cardioembolism (17%); etiology remained unknown in approximately 40% of these strokes. All the women received prophylactic treatment (antiplatelet therapy, low molecular weight heparin, or both) at the time of index pregnancy and puerperium. The mean interval between previous stroke and index pregnancy was 6.2 years (Crovetto et al 2012).

Based on data from the American Heart Association and American Stroke Association's Get with the Guidelines Stroke Registry (GWTG-Stroke), 24,641 female patients aged 18 to 44 years were identified with a cerebral infarct from 2008 to 2013: 338 of these patients (1.3%) had a stroke during pregnancy or the postpartum period (45% antepartum, 52% postpartum, and the remainder during delivery). Compared with their nonpregnant counterparts, the pregnant and postpartum patients were younger and did not have the traditional stroke risk factors. Pregnant and postpartum stroke patients had more severe strokes compared with nonpregnant patients, with median NIHSS scores of 13 and 9, respectively. There was no difference in acute stroke reperfusion therapy between the 2 groups. Symptomatic intracranial hemorrhage associated with intravenous thrombolysis was higher in pregnant and postpartum patients than in nonpregnant patients, with rates of 7.5% versus 2.6%, respectively. Despite this higher rate of intracranial hemorrhages, there was no difference in short-term outcome discharges (in-hospital mortality, discharge to home, or independent ambulation at discharge) between the 2 groups (Leffert et al 2016).

Table 8. Etiologies of Stroke in Pregnancy
Ischemic
- Thromboembolic occlusive disease
- Cardioembolic
  - Peripartum cardiomyopathy
  - Mitral valve prolapsed
  - Prosthetic heart valves
  - Atrial fibrillation
  - Rheumatic heart disease
  - Bacterial endocarditis
  - Nonbacterial (marantic) endocarditis
  - Paradoxic embolism
- Rare embolic etiologies
- Amniotic fluid
- Air
- Arterial hypotension
- Border-zone infarction
- Sheehan syndrome
- Hematologic disorders
  - Disseminated intravascular coagulation
  - Thrombotic thrombocytopenic purpura
  - Sickle cell disease
  - Arteriopathies and arteritis
  - Fibromuscular dysplasia
  - Systemic lupus erythematosus
  - "Isolated" cerebral angiitis
  - dAVF
- Cerebral venous sinus thrombosis
- Hypercoagulable state
- Infectious
- Cryptogenic
- Intraparenchymal hemorrhage
- Eclampsia
- Hypertension (other causes)
- Cerebral venous sinus thrombosis
- Arteriovenous malformation
- Vasculitis
- Choriocarcinoma
- Subarachnoid hemorrhage
- Aneurysm

Adapted from (Dafer and Biller 2009)

Anesthesia
Anesthesia issues must be individualized according to the pathophysiology of the patient's stroke. Individuals at risk for increased intracranial pressure should be identified and managed accordingly.

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**References especially recommended by the author or editor for general reading.

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**ICD and OMIM codes**

**ICD codes**

ICD-9:
Cerebrovascular disease: 431.00-438.00
Other phlebitis and thrombosis in pregnancy and the puerperium: 671.50-671.54
Cerebrovascular disorders in the puerperium: 674.00-674.04

ICD-10:
Cerebrovascular diseases: I60-I69
Venous complications in pregnancy: Q22
Venous complication in the puerperium, unspecified: O87.9

**OMIM numbers**

Ischemic stroke: #601367
Susceptibility to stroke, 1: %606799

**Profile**

**Age range of presentation**

13-18 years
19-44 years

**Sex preponderance**
male=female

**Family history**

family history may be obtained

**Heredity**

heredity may be a factor

**Population groups selectively affected**

none selectively affected

**Occupation groups selectively affected**

none selectively affected

**Differential diagnosis list**

- acute subdural hematoma
- acute vestibular syndrome
- atherosclerosis
- basilar and hemiplegic migraines
- brachial neuritis
- brain metastases
- brain tumor
- carotid and vertebral artery dissection
- central neurologic complications of pregnancy
- cerebral arteriopathies
- cerebral contusions
- cerebral vasoconstriction syndromes
- cervical disc disease
- cerebral embolism
- cerebral venous thrombosis
- complications of parenteral nutrition
- conversion disorder
- diabetic ketoacidosis
- drug-induced cerebrovascular disease
- encephalitis
- epilepsy partialis continua of Kozhevnikov
- Fabry disease
- fibromuscular dysplasia
- focal seizures
- hemiplegic migraine
- hypercoagulable states and cerebrovascular disease
- hyperglycemic hyperosmolar nonketotic state
- hyperhomocysteinemia
- hypoglycemia
- infective endocarditis
- low-grade gliomas (astrocytomas)
- malignant astrocytomas
- MELAS
- migraine with prolonged aura
- migrainous infarction
- moyamoya disease
- multiple sclerosis
- neurologic complications of chiropractic manipulation
neuromuscular junction disorders
neuropathy
neurovascular trauma
periodic paralysis
pilocytic astrocytoma in adults
pregnancy and stroke
radial neuropathy
radiculopathy
hematologic disease
oral contraceptives and stroke
pregnancy and stroke
Sneddon syndrome
stroke associated with drug abuse
stroke associated with sickle cell disease
subdural hematoma
Takayasu disease
vertebral artery dissections
Wernicke encephalopathy

Other topics to consider

Aortic atherosclerosis and stroke
Anterior cerebral artery stroke syndromes
Cerebral arteriopathies
Cerebrovascular complications of cancer
Depression after stroke
Hemorrhagic transformation of ischemic stroke
Hormonal contraception and stroke
Intracranial atherosclerosis
Ischemic stroke
Lacunar infarction
Medical complications of stroke
Reversible cerebral vasoconstriction syndromes
Stroke associated with atrial fibrillation
Stroke associated with cerebral angiography
Stroke associated with myocardial infarction
Stroke: supportive care
Stroke therapy
TIAs (carotid)
Vertebrobasilar transient ischemic attacks

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