Stroke: causes and clinical features

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Abstract
Stroke is a clinically defined syndrome of acute, focal neurological deficit attributed to vascular injury (infarction, haemorrhage) of the central nervous system. it is the second leading cause of death and disability worldwide. Stroke is not a single disease but is caused by a wide range of risk factors, disease processes and mechanisms. Hypertension is the most important modifiable risk factor, although its contribution differs for different subtypes. Most (85%) strokes are ischaemic, predominantly caused by small vessel arteriolosclerosis, cardioembolism and large artery athero-thromboembolism. Ischaemic strokes in younger patients can result from a different spectrum of causes such as extracranial dissection. Approximately 15% of strokes worldwide are the result of intracerebral haemorrhage, which can be deep (basal ganglia, brainstem), cerebellar or lobar. Deep haemorrhages usually result from deep perforator (hypertensive) arteriopathy (arteriolosclerosis), while lobar haemorrhages are mainly caused by cerebral amyloid angiopathy or arteriolosclerosis. A minority (about 20%) of intracerebral haemorrhages are caused by macrovascular lesions (vascular malformations, aneurysms, cavernomas), venous sinus thrombosis or rarer causes; these are particularly important in young patients (<50 years). Knowledge of vascular and cerebral anatomy is important in localizing strokes and understanding their mechanisms. This guides rational acute management, investigation and secondary prevention.

Keywords
Cerebrovascular disease; intracerebral haemorrhage; ischaemic stroke; MRCP; stroke pathogenesis; stroke risk factors; transient ischaemic attack

Key points
•Stroke is a clinically defined syndrome of acute, focal neurological deficit attributed to vascular injury (infarction, haemorrhage) of the central nervous system; neuroimaging is increasingly used to confirm the exact pattern of tissue injury
•Hypertension is the most important modifiable risk factor for stroke overall (although it probably contributes to different extents depending on the stroke mechanism)
•Approximately 85% of strokes are ischaemic and are caused by cerebral small vessel disease, cardioembolism and large artery atherosclerosis-related thromboembolism
•About 15% of strokes are caused by intracerebral haemorrhage, which can be deep or lobar; 80% of these result from cerebral small vessel diseases (deep perforator arteriopathy (also termed arteriolosclerosis or hypertensive arteriopathy), cerebral amyloid angiopathy or both)
•Stroke in adults <50 years old accounts for about 15% of cases and can result from a different spectrum of diverse causes compared with older individuals, including extracranial dissection

Epidemiology
Stroke is a huge and increasing global health challenge. Worldwide, stroke is the leading cause of acquired physical disability in adults, and the second leading cause of mortality in middle- to high-income countries. In such countries, the overall incidence of ischaemic and haemorrhagic stroke has risen over the last decade to 85–94 per 100,000, but is much higher (1151–1216 per 100,000) in people >75 years old. Moreover, 85% of all stroke deaths occur in low-income countries, and also account for 87% of stroke-related disability-adjusted life–years.

In the UK, stroke results in aggregate societal costs (including hospital, formal and unpaid care sectors) of £26 billion a year, with stroke care accounting for approximately 5% of total National

Health Service costs. Cerebrovascular disease is the leading cause of epilepsy in elderly individuals, and the second most common cause of late-onset dementia.

Definitions

It is important to recognize that stroke and transient ischaemic attack (TIA) are clinical syndromes and that the underlying vascular brain injury can have many different mechanisms (associated with different risk factors and disease processes; Figure 1). Thus 'stroke' and 'TIA' are not single or complete diagnoses, but a starting point for rational investigation and treatment.

Transient ischaemic attack and stroke: a TIA is traditionally defined as a brief episode of focal neurological dysfunction not associated with permanent cerebral infarction, and lasting *less than* 24 hours. Stroke is defined as focal neurological deficit of sudden onset, with symptoms lasting *more than* 24 hours (or resulting in death before 24 hours). These definitions are no longer helpful in clinical practice for the following reasons: treatment of stroke is time sensitive and needs to be commenced as soon as possible after diagnosis; the 24-hour time boundary is arbitrary; and 30–50% of patients with clinically defined TIAs have evidence of brain ischaemia or infarction on diffusion-weighted magnetic resonance imaging (MRI). It is also increasingly recognized that some 'atypical' attacks not classical for TIA can also be associated with cerebral ischaemia on brain imaging.

Attacks of recurrent, stereotyped paraesthesia and numbness (usually spreading across contiguous body areas including the hand and face over several minutes) in older people are associated with convexity subarachnoid haemorrhage resulting from cerebral amyloid angiopathy (CAA), and therefore mandate brain imaging, ideally with MRI. With the increasing availability of MRI, imaging-based definitions of TIA and stroke will probably take precedence in the future. The term 'cerebrovascular accident' or 'CVA' is outdated, inaccurate, encourages therapeutic nihilism, and should no longer be used.

Classification of stroke

The Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification system is the most widely used mechanistic subclassification system for patients with cerebral ischaemia, defining five subtypes: (1) large artery atherosclerosis, (2) cardioembolic, (3) small vessel occlusion, (4) stroke of other determined aetiology, and (5) stroke of undetermined aetiology.[1] In the more recent phenotype-based A-S-C-O system, every patient is classified according to the relative contribution of Atherosclerosis, Small vessel disease, Cardiac source and Other causes. The value of this additional complexity has not been established in clinical practice.

There is less consensus on classifying spontaneous (non-traumatic) intracerebral haemorrhage (ICH; bleeding into the brain substance). One system, SMASH-U, categorizes causes as Structural vascular lesions, Medication, Amyloid angiopathy, Systemic disease, Hypertension or Undetermined. However, these categories are a mixture of risk factors, mechanisms and disease processes. A recently proposed classification system, CLAS-ICH, includes neuro-imaging markers of the underlying causal vascular process – macrovascular lesions (e.g. arteriovenous malformations, aneurysms), or cerebral small vessel diseases (CSVD; including arteriolosclerosis or CAA) . Other forms of intracranial bleeding (subdural, extradural, subarachnoid) are not considered in this article.

Risk factors for stroke[2]

Non-modifiable risk factors

Age: this is the most important contributor to stroke risk. The incidence doubles for each decade after age 55 years.

Sex: because of the risks of pregnancy and oral contraceptive use, premenopausal women have a stroke risk that is as high as or higher than that in men. At older ages stroke rates are slightly higher in men. Overall in the UK, more women than men have strokes.

Ethnicity: African Caribbean individuals in the UK and USA have twice the risk of incident stroke as their white counterparts. In younger black adults the risk of ICH is twice that of age-matched white people. This may in part relate to the increased prevalence of stroke risk factors, such as uncontrolled hypertension, obesity and diabetes, among African Caribbean populations. Other ethnicity-related risks contributing to stroke include carotid stenosis in white individuals, metabolic syndrome in South Asian and Pacific Islander groups, and increased rates of intracranial stenosis and ICH in East Asian populations.

Genetics: in addition to the single-gene disorders that are associated with stroke (CADASIL, CARASIL, Fabry disease, homocystinuria, sickle cell disease, connective tissue disorders; Table 1), the MEGASTROKE consortium identified 32 genome-wide significant loci, 22 of which were novel.[3] Some loci were strongly linked to particular stroke mechanisms (e.g. large artery disease, small artery disease, cardiac embolism), while half the loci showed a shared genetic association with other vascular pathologies, the largest correlation being for blood pressure.

Modifiable risk factors

Hypertension: this is the most important modifiable risk factor overall for stroke. Approximately half of all stroke patients, and an even greater proportion of those with ICH, have a history of hypertension. Even among those not defined as hypertensive, the higher the blood pressure, the higher the risk of stroke. This makes the diagnosis and control of hypertension paramount for primary and secondary prevention of strokes. The attributable risk from hypertension declines after age 60 years, where it confers relative risk of 3.5, to a non-significant contribution at age 80.

Diabetes mellitus: this is an independent risk factor for stroke, associated with a 2-fold increased risk. Stroke accounts for 20% of all deaths in people with diabetes.

Cardiac factors: cardioembolic infarction (mainly from atrial fibrillation (AF)) is the most severe ischaemic stroke subtype, with high disability and mortality. The presence of AF increases with age, causing 20–25% of strokes in patients >80 years old. Anticoagulation is extremely effective in preventing stroke in people with AF (relative risk reduction about two-thirds).

Smoking: this doubles the risk of stroke. Smoking cessation rapidly reduces the risk, with excess risk nearly disappearing 2–4 years after stopping.

Hyperlipidaemia: the relationship between dyslipidaemia and stroke is complex. There is an increased risk of ischaemic stroke with increased total cholesterol, and a decreased risk of ischaemic stroke with elevated high-density lipoprotein-cholesterol. In contrast, total cholesterol is inversely associated to risk of ICH. The use of statins in secondary prevention appears to reduce the risk of ischaemic stroke (as well as functional outcome and mortality) with no definite increase in the risk of ICH. Current evidence and expert opinion favours offering statins to survivors of ICH who have a strong indication for their use (e.g. clinically relevant ischaemic heart disease).

Alcohol consumption and substance abuse: light and moderate alcohol consumption (<4 units/day) has been reported to be associated with a lower risk of ischaemic stroke, whereas higher quantities are clearly associated with increased stroke risk. Alcohol consumption has a linear relationship with ICH risk. Recreational drugs including cocaine, heroin, amphetamines, cannabis and ecstasy are associated with an increased risk of stroke (both ischaemic stroke and ICH).

Obesity and sedentary behaviour: most of the effect of body mass index on stroke risk is mediated by blood pressure, cholesterol and glucose concentrations. People who are physically active have a lower risk of stroke and overall stroke mortality than those who are inactive.

Inflammation: raised inflammatory biomarkers have a modest association with increased risk of arteriosclerosis and stroke. Infection can trigger stroke, and there is evidence that stroke rates are lower in individuals vaccinated against influenza. Coronavirus disease (COVID-19) has been linked to large vessel occlusions in association with a hyperinflammatory and hypercoagulable state.

Pathogenesis of stroke

Stroke in the young: about 10–15% of all strokes occur in adults aged 25–49 years. Table 1 contains a list of stroke aetiologies to consider in this population. Extracranial carotid or vertebral dissection is common and important to consider but should be actively sought through the history, examination and neuro-imaging. Cardiac causes (e.g. patent foramen ovale, rhythm disturbances, endocarditis), recreational drugs and thrombophilias are also important to seek in unexplained strokes in younger people.

Ischaemic stroke: approximately 85% of strokes are ischaemic, predominantly the result of CSVD, cardioembolism (mainly AF) or large artery disease (atherosclerosis).

Cerebral small vessel disease: CSVD includes arteriosclerosis (also termed deep perforator arteriopathy or hypertensive arteriopathy) and CAA. Arteriolosclerosis affects the structure and function of small vessels (usually in the range of hundreds of microns) supplying the basal ganglia, deep white matter and brainstem; it causes approximately 25% of ischaemic strokes and 80% of non-traumatic ICH, and contributes to about 45% of dementia (Figure 2a). CAA also affects small vessels (mainly superficial leptomeningeal or cortical arterioles near the brain surface) but is considered separately as a more important cause of ICH than ischaemic stroke (see below).

CSVD is diagnosed on the basis of radiological markers, including recent small subcortical infarcts, white matter hyperintensities, lacunes, cerebral microbleeds, enlarged perivascular spaces and cerebral atrophy on MRI, or white matter hypodensities and lacunes on computed tomography (CT). Its prevalence increases with age with no apparent differences between sexes, and can be higher in Asian populations. The most important risk factor for CSVD is hypertension. More rarely, genetic disorders (Table 1), radiation exposure and immune-mediated vasculitides can cause CSVD.

Cardioembolic stroke: a further 25% of ischaemic strokes are caused by cardioembolic disease (mainly AF), the risk increasing with age. In patients with stroke, paroxysmal AF is more prevalent than persistent AF. Post-stroke AF is found in approximately 8% of individuals presenting to accident and emergency with a stroke, 11% of those using 24–72-hour Holter monitoring and 17% of those using external or implanted loop recording; however, the clinical significance of short runs (<30 seconds) of AF is uncertain. Other rarer causes of cardiac embolism are detailed in Table 1.

Large artery disease: stenosis or occlusion of the large cerebral arteries (predominantly the extracranial carotid) is the cause of about 20% of ischaemic strokes (Figure 2b).

Rupture of arteriosclerotic plaques leads to *in situ* thrombus formation and distal embolization. In addition, ruptured carotid plaques lead to widespread platelet activation, and recurrent events are very common, particularly in the first few weeks. Less commonly, stenosis of the vertebrobasilar or intracranial arteries causes ischaemic strokes. Haemodynamic strokes can occur when the systemic blood pressure drops in the context of arterial stenosis, leading to infarction of border zone territories. Extracranial dissections of cervico-cephalic arteries (sometimes traumatic) account for about 1 in 5 ischaemic strokes in patients <50 years old.

Cryptogenic stroke: in 20–30% of patients with ischaemic stroke, no cause is found. These strokes can relate to undiagnosed cardioembolic disease, hypercoagulable states, paradoxical emboli via a patent foramen ovale, sub-stenotic atheromatous disease, non-atherosclerotic arteriopathies, occult recreational drug use or undiagnosed genetic conditions or risks.

Intracerebral haemorrhage: spontaneous (non-traumatic) ICH can be anatomically divided into lobar and non-lobar (deep or infratentorial) (Figure 3). Non-lobar haemorrhages account for approximately two-thirds of ICH cases, and occur in the basal ganglia and internal capsule (35–70%) or brainstem (5–10%). About 5–10% of ICHs are in the cerebellum. The remainder are lobar haemorrhages located in cortico-subcortical areas in the cerebral lobes, often near or reaching the cerebral convexities.

Arteriolosclerosis (also termed hypertensive or deep perforator arteriopathy) is the most important cause of non-lobar ICH, although it also contributes to lobar ICH. The term ‘hypertensive intracerebral haemorrhage’ is unhelpful because hypertension is neither necessary nor sufficient to cause most ICH. Detection of the neuro-imaging markers of CSVD mentioned above (including cerebral microbleeds) can help increase confidence that an ICH has been caused by CSVD.

CAA – a CSVD characterized by the presence of amyloid-β protein within the cortical and leptomeningeal blood vessel walls – is an important cause of lobar (but not non-lobar) ICH in older people.[4] CAA is also associated with cognitive impairment, transient focal neurological episodes; these are usually recurrent stereotyped attacks of spreading paraesthesias affecting the arm and face, lasting a few minutes to half an hour, occurring over days to a week or two, and often related to small convexity subarachnoid haemorrhages. CAA can be diagnosed by brain imaging showing haemorrhage restricted to the lobar brain regions (Figure 3c).

The 80% of all ICH caused by CVSD is often termed ‘primary intracerebral haemorrahge’, but this term is not well defined, discourages adequate investigation, classification or rational secondary prevention, and is thus not recommended. The next most common cause of ICH after CSVD is a range of macrovascular abnormalities (arteriovenous malformations, dural arteriovenous fistulae, aneurysms); these are more common in (but are not limited to) younger people and can only be identified by imaging of the brain vessels (e.g. CT angiography, MR angiography, digital subtraction intra-arterial angiography). Rarer causes of ICH include haemorrhagic infarction caused by cerebral

venous sinus thrombosis, brain tumours, reversible cerebral vasoconstriction syndrome and endocarditis (Figure 3). Recreational drug use (especially cocaine) increasingly contributes to ICH in younger people.

Stroke localization

Knowledge of intracranial vascular territories and neuroanatomical pathways allows the localization of lesions with relevance for interpreting brain imaging and understanding the functional deficit, prognosis and mechanism of stroke (Table 2). ICH cannot be reliably differentiated from ischaemic stroke without imaging.

Anterior circulation: this comprises territories supplied by the anterior and middle cerebral arteries, which are branches of the internal carotid artery. The first branch of the internal carotid is the ophthalmic artery. Carotid thromboembolic disease resulting from carotid atherosclerosis can thus lead to amaurosis fugax (transient monocular loss of vision) in the affected eye. A full proximal occlusion of the middle cerebral artery (often from a cardiac embolus) typically causes contralateral hemiparesis and hemisensory loss (see Figure 2c), a homonymous visual field defect, hemineglect and (if in the dominant hemisphere) aphasia.

Involvement of the superior division of the middle cerebral artery produces contralateral hemiplegia, hemisensory loss and, on the dominant side, a non-fluent (Broca) aphasia. Involvement of the inferior division often produces a contralateral hemianopia and, if left-sided, a fluent (Wernicke) aphasia. If more distal branches are involved the territory of neurological deficit becomes more limited (the extreme of this being a ‘cortical hand’ syndrome caused by infarction of primary sensorimotor cortex).

Vertebrobasilar circulation: the right and left vertebral arteries join to form the basilar artery, which divides to form the posterior cerebral arteries. These supply the occipital cortex, so that infarction leads to hemianopia. Strokes in the vertebrobasilar territory are a diagnostic challenge because of the large number of clinical syndromes they can present with (Table 2).[5] For example, brainstem ischaemia can lead to ‘crossed’ signs, while basilar ischaemia can result in bilateral hemiparesis, sensory loss, visual disturbance and ‘locked-in’ syndrome.

Small vessel occlusions (small subcortical infarcts): small subcortical infarcts caused by occlusion of small perforating arteries are often asymptomatic, but produce ‘lacunar syndromes’ when they occur in eloquent brain areas. The most common lacunar syndromes (and corresponding infarct locations) are pure motor stroke (posterior limb of the internal capsule), pure sensory stroke (lateral thalamus), sensorimotor stroke (thalamo-capsular region), dysarthria–clumsy hand syndrome (usually pons) and ataxic hemiparesis (posterior internal capsule, pons, centrum semiovale). The progression of CSVD with accumulation of small subcortical infarcts and progressive white matter damage causes a typical clinical syndrome of progressive cognitive impairment (typically dominated by executive dysfunction and slow processing) and gait disturbance (apraxia, reduced stride length and falls).

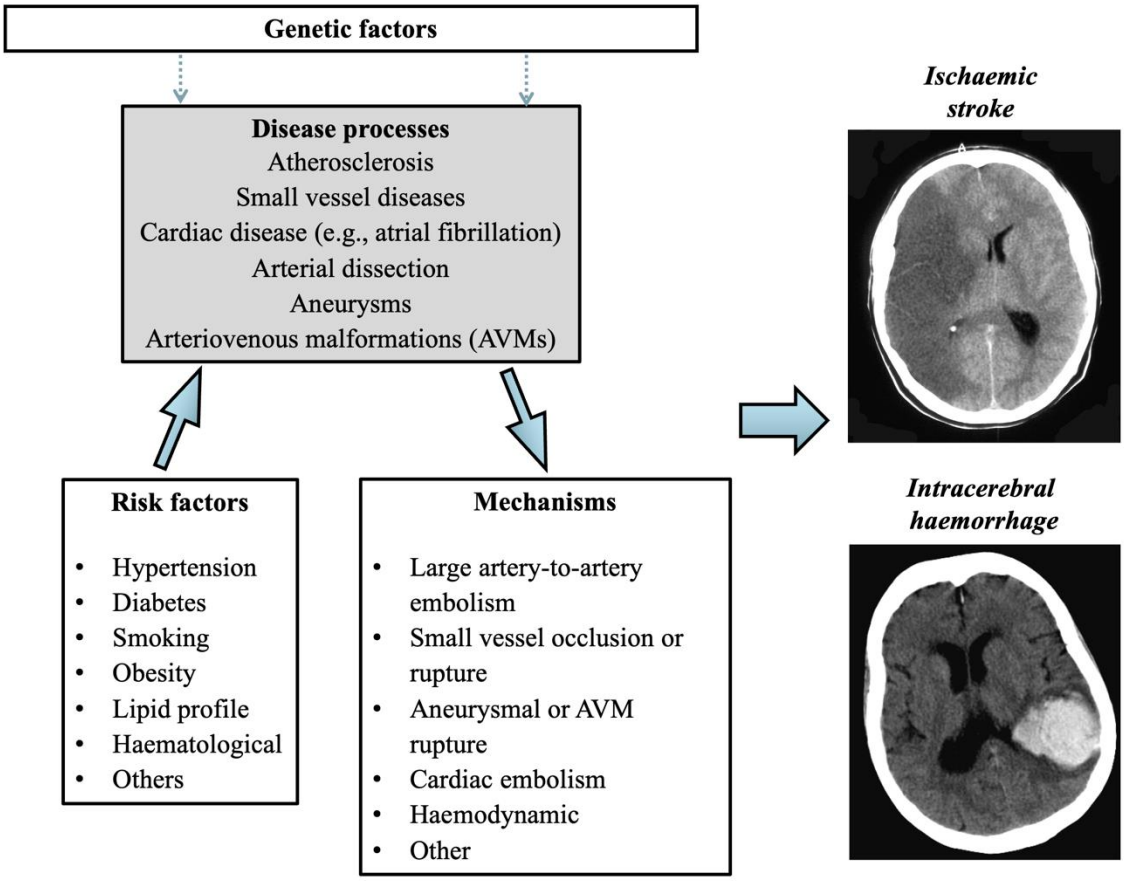
Genetic factors
Disease processes
Atherosclerosis
Small vessel diseases
Cardiac disease (e.g., atrial fibrillation)
Arterial dissection
Aneurysms
Arteriovenous malformations (AVMs)
Risk factors
Hypertension
Diabetes
Smoking
Obesity
Lipid profile
Haematological
Others
Mechanisms
Large artery-to-artery embolism
Small vessel occlusion or rupture
Aneurysmal or AVM rupture
Cardiac embolism
Haemodynamic
Other
Ischaemic stroke
Intracerebral haemorrhage

Figure 1

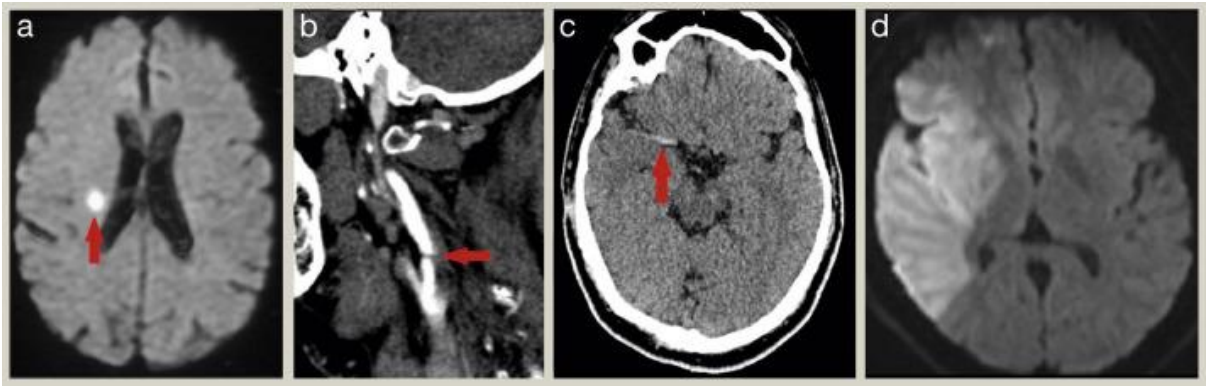

Figure 2. (**a**) Axial diffusion-weighted MRI showing an acute small subcortical infarction in the right centrum semiovale white matter consistent with a small vessel occlusion (red arrow). (**b**) Extracranial CT angiography demonstrating ≥95% carotid stenosis (red arrow). (**c**) Non-contrast axial CT of the brain showing acute thrombus in the right middle cerebral artery (the hyperdense MCA sign; red arrow). (**d**) Resulting acute infarction showing high signal indicating restricted diffusion on axial diffusion-weighted MRI of the brain.

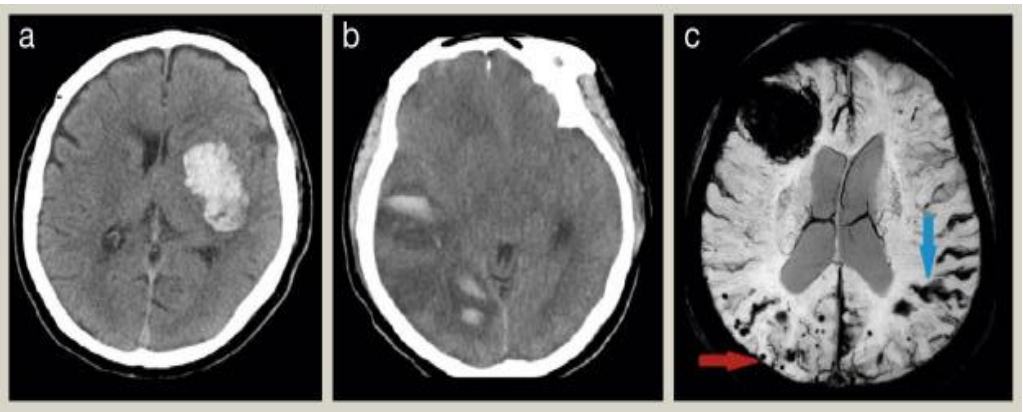

Figure 3. (**a**) Non-contrast axial CT scan showing a deep ICH in the basal ganglia. (**b**) Non-contrast axial CT scan showing venous haemorrhagic infarction of the right temporoparietal region caused by a right transverse cerebral venous sinus thrombosis. (**c**) Susceptibility-weighted imaging showing lobar haemorrhage, superficial haemosiderin staining within and around the cerebral sulci (cortical superficial siderosis; blue arrow), and strictly lobar parenchymal microbleeds (red arrow) consistent with CAA.

Potential mechanisms of stroke in younger patients

Haematological conditions	Protein C/S/antithrombin III deficiency (venous risk only) Prothrombin/factor V Leiden mutations (venous risk only) Acquired prothrombotic states (**pregnancy, oral contraceptive use**, cancer, nephrotic syndrome, anabolic steroid use, **antiphospholipid syndrome**) Myeloproliferative disorders
Inflammatory	Primary central nervous angiitis, granulomatosis with polyangiitis, Sjögren syndrome, Takayasu arteritis
Genetic	**CADASIL**, CARASIL, **Fabry disease**, MELAS, homocystinuria, **sickle cell disease**, connective tissue/collagen vascular disorders
Vascular (non-arteriosclerotic)	**Extracranial arterial dissection**, Susac syndrome, reversible cerebral vasoconstriction syndrome, Sneddon syndrome, migrainous infarction, fibromuscular dysplasia, moyamoya disease
Cardiac	**AF**, **infective endocarditis**, **paradoxical embolization through a patent foramen ovale**, atrial tumours
Infective diseases	Syphilis, varicella zoster vasculopathy, tuberculous meningitis, **HIV,** possibly coronaviruses
Recreational drugs	Cannabis, **cocaine**, opiates, amphetamines, MDMA, γ-hydroxybutyrate

Selected more common or important causes are in bold.

CADASIL, Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leucoencephalopathy; CARASIL, Cerebral Autosomal Recessive Arteriopathy with Subcortical Infarcts and Leucoencephalopathy; MELAS, Mitochondrial Encephalopathy, Lactic Acidosis, and Stroke-like episodes. Note that MELAS causes stroke-like attacks rather than conventional ischaemic stroke.

Table 1.

Clinical localization of stroke by vascular territory

Anterior cerebral artery
•Leg more than arm involvement with hand sparing
•Urinary incontinence
•Gait apraxia
•Akinetic mutism
Middle cerebral artery
•Homonymous hemianopia/quadrantanopia (often resulting from involvement of the inferior division)
•Face–arm–leg involvement (affected territory reduces as the site of occlusion becomes more distal)
•Aphasia (Broca = superior division; Wernicke = inferior division)
•Inattention
•Gaze paralysis (usually indicates a large area of frontal damage)
Vertebrobasilar
•Occipital lobe – homonymous hemianopia, cortical blindness, other cortical visual deficits
•Cerebellum – ataxia, nystagmus
•Brainstem cranial nerve palsies – diplopia, facial numbness/weakness, vertigo, dysphagia, dysphonia
•Spinal tracts – hemiparesis and hemisensory loss
Lacunar stroke syndromes (caused by occlusion of deep perforating small arteries)
•Pure motor hemiparesis
•Pure sensory stroke
•Sensorimotor stroke
•Ataxic hemiparesis

Table 2.

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