How to approach the diagnosis of uncommon causes of ischaemic stroke

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Abstract

Stroke is a common neurological emergency and although the majority of cases are associated with traditional vascular risk factors leading to cerebral ischaemia by well-recognised pathophysiological mechanisms, around 4% of ischaemic stroke cases are due to rare conditions. These are important to recognise due to the different management, which is often specific and effective, and prognosis from otherwise cryptogenic ischaemic strokes. We outline a practical approach to identifying uncommon causes of ischaemic stroke by highlighting diagnostic ‘red flags’ and propose a structured approach to investigating them.

Key points

- The same principles apply to investigating rare causes of ischaemic stroke as with other aspects of neurological practice; when a diagnosis is not forthcoming, continually revisit the history and investigations
- Rare causes of stroke are not reserved for the young
- Be cautious to conclude a condition is the sole aetiology when there is only an association rather than a direct pathophysiological link to ischaemic stroke
- Do not hesitate to collaborate with the multidisciplinary team, particularly neuroradiology, infectious diseases, rheumatology and genetics.

Further reading

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Introduction

Ischaemic stroke is a common neurological emergency; more than 90% of cases are associated with conventional vascular risk factors[1] and can be categorised into major aetiological categories including cardioembolism (most commonly atrial fibrillation), athero-thrombo-embolism (from large artery atherosclerosis), and sporadic cerebral small vessel disease. However, up to a third of cases remain undetermined (cryptogenic) despite systematic and standardised investigation.[2,3]

Uncommon causes of ischaemic stroke that do not fit into these major categories (termed 'other determined stroke'[2]) account for around 4% of cases (*Table 1*).[4] These conditions are overrepresented in the young (<50 years), partly because conventional vascular risk factors become more prevalent with age. Nevertheless, traditional vascular risk factors also remain common in young ischaemic stroke patients; in one large case-control study, physical inactivity, hypertension, alcohol excess and smoking accounted for 80% of the population attributable risk for stroke in young adults.[5]

Diagnosing uncommon causes of ischaemic stroke poses a challenge for neurologists and stroke physicians since even those in busy stroke services may only see one or two such cases a year. However, the importance of an accurate diagnosis cannot be overstated given the implications for prognosis and management for what would otherwise be diagnosed as a 'cryptogenic' ischaemic stroke.

The typical presentation and initial investigation of acute ischaemic stroke has been described in a previous article in this series.[6] In this article we outline a practical approach to diagnosing uncommon causes of ischaemic stroke by highlighting 'red flags' in the history, examination and initial investigations; for the patients so identified, we also propose a structured approach to investigations beyond the 'standard' ischaemic stroke work-up. We focus on conditions that have a direct and proven mechanistic association with ischaemic stroke, but will not dwell on patent foramen ovale[7] and cerebral venous sinus thrombosis (CVST; including both cerebral venous sinus thrombosis and cortical vein thrombosis), which have both recently been reviewed in *Practical Neurology*.[8] Furthermore, monogenic causes of ischaemic stroke will be addressed in a forthcoming article in this series so will not be covered in detail.

History

Certain aspects of the patient's background and presenting history may provide the first indication of an uncommon ischaemic stroke aetiology.

Background

The patient's age and vascular risk factor profile are key contextual factors. Around 10-15% of ischaemic stroke patients are aged 18-50 years and a lack of conventional vascular risk factors should be considered a 'red flag' for a rarer cause.[9] Note that a particular set of risk factors for ischaemic stroke exist in women of child-bearing age, including oestrogen-based hormonal contraception and migraine with aura.[10,11] However, although age is a strong vascular risk factor, it should not be forgotten that older patients can also have uncommon causes of ischaemic stroke. Specific historical aspects may also offer pointers to aetiology, for example difficult to control hypertension at a young age may prompt consideration of underlying secondary causes (for example phaeochromocytoma, renal artery stenosis, or Fabry disease) and, notably in young women, past spontaneous coronary artery dissection, or venous thromboembolism or miscarriage, may raise the possibility of fibromuscular dysplasia or antiphospholipid syndrome, respectively.

Specific comorbidities associated directly with ischaemic stroke mechanisms include malignancy (*Box 1*), autoimmune conditions, systemic vasculopathies and haematological diseases (*Table 1*).

Recent history

Prodromal constitutional symptoms may suggest an underlying infectious, inflammatory or malignant process. Fever on admission most commonly indicates acute infection, which is a well-established trigger for ischaemic stroke via a range of mechanisms.[12,13] Around 20% of acute stroke patients present with pneumonia, an important risk factor, consequence and determinant of outcome in ischaemic stroke.[14–16] Recent COVID-19 infection is an important and topical cause of ischaemic stroke, possibly moreso than other respiratory viruses,[17] via multiple potential mechanisms including an exaggerated inflammatory response, endothelial dysfunction, platelet activation and hypercoagulability.[18] However, ischaemic stroke can occasionally occur

as a result of direct central nervous system (CNS) infection, as indicated by fever, meningism, seizures or encephalopathy. Patients should therefore be directly asked about sexual history (*Box 2* for HIV-associated stroke), and the past 5 years of travel, including potential exposure to ticks.

Subacute bacterial endocarditis (SBE) should be considered in patients with a febrile or constitutional prodrome and known cardiac valvular pathology, intravenous recreational drug use or risk of an enteric organism bacteraemia (such as inflammatory bowel conditions, gastrointestinal tract instrumentation or poor dental hygiene). Around one-fifth of patients with SBE suffer ischaemic stroke or TIA due to embolism of valvular vegetations.[19] Prompt recognition of SBE is vital as thrombolysis carries a high risk of haemorrhagic transformation and the presence of mycotic aneurysms complicates the use of antiplatelets and anticoagulation. Early institution of antibiotic therapy is the most effective treatment.[20]

Progressive stroke syndromes or early recurrence without explanation should instigate investigation for an underlying infectious, inflammatory or malignant process. Prodromal psychiatric symptoms or subacute cognitive decline should prompt consideration of inflammatory vasculopathies, such as primary angiitis of the CNS (PACNS), SLE, HIV vasculopathy, syphilis, or genetic aetiologies such as *cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy* (CADASIL) *cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy* (CARASIL) or *mitochondrial encephalopathy with lactic acidosis and stroke-like episodes* (MELAS).

Presenting features

The patient's activity at symptom onset may provide an insight to stroke mechanism, for example neck manipulation or trauma (cervical artery dissection), or Valsalva (paradoxical embolism via a patent foramen ovale). As these are relatively common causes of ischaemic stroke, particularly in the context of risk factors for venous thromboembolism in the latter,[7] they are not discussed further in this article.

Headache at symptom onset is traditionally associated with intracerebral haemorrhage (ICH), but can be seen in infarcts, particularly in the posterior circulation.[21] Headache is the most common presenting symptom of CVST[8] and features in approximately half of patients with PACNS. Although the former may be

associated with features of raised intracranial pressure, there are often no particular distinguishing features. By contrast, recurrent spontaneous or provoked (by sexual intercourse, exercise or emotion) thunderclap headache is highly characteristic of reversible vasoconstriction syndrome (RCVS).[22] Headache or scalp tenderness in patients ≥50 years old with retinal ischaemia or (particularly posterior circulation) TIA should prompt consideration of giant-cell arteritis. Similarly, patients presenting with severe unilateral head, face or neck pain at symptom onset, particularly younger patients, is highly suggestive of cervical dissection which can present weeks after a provoking activity.

Seizures as a presenting feature should act as a 'red flag' as they occur in only around 5% of patients with acute ischaemic stroke.[23] Focal or generalised seizures occur in around one-third of patients with CVST, particularly those with parenchymal lesions and cortical vein thrombosis.[24] Other infectious or inflammatory conditions with cortical involvement (e.g. herpes, other forms of encephalitis or autoimmune encephalitis) should also be considered, and seizures are common in MELAS.

Drug history

Details of prescription, over-the-counter, and illicit drug use should be sought. Use of vasoactive medications (cough and cold suppressants, selective serotonin reuptake inhibitors, triptans, chemotherapy agents[25]) and recurrent thunderclap headache is strongly indicative of RCVS. Drugs of abuse, particularly cocaine and amphetamines, can cause ischaemic stroke or intracerebral haemorrhage. Proposed mechanisms include a sympathomimetic effect leading to hypertension and vasoconstriction, cardiac arrhythmia, prothrombotic states or vasculopathy.[26]

Family history

A family history of stroke in young age is mainly pertinent to monogenic causes of stroke, covered in a future article. Consanguinity can be a clue to recessive diseases and predominantly affected males may indicate an x-linked disorder (*Table 1*). Red flags may be early onset dementia, diabetes, hearing impairment, or a strong family history of autoimmune diseases.

Examination

Whilst the neurological examination is important in defining the stroke syndrome (for example multifocal cortical infarcts or a lacunar syndrome) which can provide mechanistic insight, it is often of limited benefit in diagnosing an uncommon aetiology. By contrast, a thorough systemic examination, with particular attention to the cardiovascular system, eyes, skin, ears, and mucous membranes, is more valuable and may provide clues to narrow the diagnostic process (*Figure 1* and *Table 2*).

Investigations

There are no validated diagnostic algorithms to guide a clinician through the vast and expensive array of investigations for rare causes of ischaemic stroke. Patients with a rare cause of ischaemic stroke will usually initially be classified as having an undetermined (cryptogenic) or embolic stroke of undetermined source. That is to say a standard stroke work-up has not been contributory; namely cardiac rhythm monitoring, imaging of the brain parenchyma and non-invasive angiography of the intracranial and cervical vasculature.[6] Patients with imaging features suggestive of an embolic source should have more thorough cardiac investigations, including prolonged cardiac monitoring, a transthoracic echocardiogram (including bubble contrast) and vascular imaging of the proximal arterial tree.

When a rare cause of ischaemic stroke is suspected, these initial results should be re-reviewed prior to further testing in order to focus subsequent investigation and potentially prevent unnecessary, expensive, and sometimes invasive, procedures. Such cases are best discussed in a multidisciplinary team setting, including neuroradiology and relevant specialty expertise from microbiology/ infectious diseases, cardiology, haematology, immunology and rheumatology, as required.

Laboratory investigations

Where the history and examination have suggested possible infective or inflammatory aetiology of an ischaemic stroke, blood laboratory investigation is often the first line in narrowing down an exact cause which, especially in the case of infection, is often desirable early in the course of presentation. Significantly elevated inflammatory markers (white cell count, C-reactive protein [CRP] or erythrocyte sedimentation rate [ESR]) may suggest underlying infection or inflammation, in particular SBE, atrial myxoma, giant cell arteritis (though CRP can be elevated rather than ESR), or a malignant process. In addition to raised inflammatory markers, patients with

autoimmune conditions or chronic infection may also exhibit a mild anaemia. For suspected SBE, serial blood cultures should be expeditiously obtained.

A thrombocytosis (platelet count >400-450x10^9/L) can either be primary (i.e. a myeloproliferative or myelodysplastic process) or secondary (i.e. reactive to infection, iron deficiency, inflammation or remote malignancy). Essential thrombocytosis is the most common condition in the former group and is associated with a particularly high risk of both arterial and venous thrombosis. Initial follow-up investigations should include a peripheral blood smear to confirm true thrombocytosis followed by iron studies and acute phase reactants to exclude a treatable cause. If a cause is not identified or the thrombocytosis persists despite treatment, the patient should be screened for malignancy and discussed with the haematology team for consideration of JAK2 mutation analysis and bone marrow assessment.[27]

Inflammatory or autoimmune systemic vasculitides may also involve other organs and be suggested by abnormal urinalysis, renal or liver function, raised inflammatory markers or a mild anaemia.

In addition to blood work up, an early lumbar puncture is indicated when CNS infection is suspected, though caution should be employed if there has been a large stroke with (potential) mass effect. Although an elevated cerebrospinal fluid (CSF) protein and pleocytosis is identified in the majority of patients with PACNS,[22] the sensitivity and specificity of CSF abnormalities in other CNS vasculitides is variable.

In the absence of specific laboratory markers of aetiology (and even when markers are positive) it is often the combination with neuroimaging that offers highest yield in determining the mechanism and aetiology of ischaemic stroke.

Imaging

Although there are few rare causes of ischaemic stroke that can be diagnosed definitively by imaging, there are several imaging characteristics that may narrow the differential diagnosis or suggest an uncommon or rare cause of stroke.

Initial non-contrast CT brain imaging may indicate multi-territorial infarcts (suggestive of a cardioembolic or vasculitic aetiology) or a non-arterial territory distribution, such as in venous infarction or mitochondrial disease. CT imaging may also demonstrate

co-existent sulcal subarachnoid haemorrhage which can be seen with intradural dissection, CVST, RCVS, and SBE due to mycotic aneurysms.

MRI is increasingly performed in the acute setting as it offers greater sensitivity in detecting acute and smaller infarcts. It can also age multiple subacute infarcts especially in the deep white matter or corpus callosum seen in subacute multifocal processes such as vasculitides or Susac's syndrome. Certain sequences such as susceptibility weighted imaging (SWI) are highly sensitive for haemorrhage, particularly sulcal/ subarachnoid haemorrhage.

The stroke-like lesions of MELAS are often transient and predominantly affect grey matter.[28] Extensive, confluent deep white matter T2 hyperintensities may suggest a monogenetic cause of stroke, such as CADASIL, particularly when involving the temporal poles, external capsule and corpus callosum.[29]

If CNS infection is suspected, contrast can be helpful to look for specific changes such as the meningeal-based enhancement seen in tuberculous meningitis that can have an associated vasculitis.

Non-invasive angiography of the cervical and intracranial arteries should be carefully reviewed for evidence of a vasculopathy. The pattern of vascular involvement can give certain clues to the aetiology. A single vessel abnormality with intramural haemorrhage suggests dissection, whereas multifocal involvement with calcification is more likely to represent atherosclerosis. Vasculitis can affect large, medium, or smaller arteries and is not always visible on non-invasive angiography; it is often worth revisiting the parenchymal imaging in conjunction with angiography. It is frequently difficult to differentiate medium to small artery vasculitis from RCVS with conventional non-invasive angiography and where available, high resolution vessel wall imaging can contribute further to the work-up (*Figure 2* and *Box 3*).[30]

Where intracranial occlusion/ narrowing has been chronic, it can be associated with the appearance of moyamoya angiopathy ('puff of smoke') which represents the fragile network of collateral arteries developing in response to progressive terminal internal carotid artery stenosis.[31] This can be an isolated, idiopathic (likely polygenic) process or secondary to cervicocranial irradiation, atherosclerosis, chronic meningitis, autoimmune vasculopathies, thrombophilia or sickle-cell disease.[32]

Further investigations

Ideally, further diagnostic work-up should be tailored to the individual patient and the 'red flags' identified in the history, examination and baseline investigations. *Table 2* outlines potential further investigations that can be undertaken as a comprehensive work-up of rare causes of ischaemic stroke.

Conclusion

Uncommon causes of ischaemic stroke should be considered in patients who do not have conventional risk factors for cerebrovascular disease or lack evidence for one of the major aetiological categories. This is particularly true in those presenting with systemic symptoms suggestive of an infective, inflammatory or malignant process. In such cases it is often necessary to repeat a thorough history and examination and re-review imaging and other investigations in a multi-disciplinary setting.

Figure legends

Figure 1: Selected examination findings in rare causes of ischaemic stroke: a) pseudoxanthoma elasticum of the antecubital fossa, b) painful ulceration of the tongue (Behçet's disease), c) angiokeratoma (Fabry disease), d) dystrophic calcinosis cutis (various connective tissue diseases). Images from DermNet NZ (www.dermnetnz.org) on 2/12/2021)

Figure 2: Spectrum of high-resolution intracranial vessel wall imaging changes across different pathologies in patients presenting with stroke and intracranial vessel narrowing. Cross-sectional angiography images (top row) show the vessel narrowing without a definitive clue to the underlying aetiology. In intracranial atherosclerosis (ICAD), at the site of luminal narrowing there is focal eccentric wall thickening with focal eccentric enhancement (yellow arrow) of an atherosclerotic plaque. In intracranial dissection, T1 before contrast shows wall thickening anteriorly with mural high signal intensity consistent with intramural blood products (white arrow); post contrast shows thin peripheral enhancement which can be variable depending on the extent of remodelling. In RCVS, no enhancement seen at the site of right superior cerebellar artery narrowing (black arrow). In this case of secondary vasculitis, there is a long segment of middle cerebral artery narrowing with circumferential enhancement of the vessel wall (golden arrow).

Table 1 *– Uncommon causes of ischaemic stroke*

Category	Condition	Comments
Autoimmune conditions and systemic vasculopathies	Systemic lupus erythematosus (SLE)	Multiple potential stroke mechanisms: cardioembolism from Libman-Sacks endocarditis; prothrombotic state; accelerated atherosclerosis, and; (rarely) CNS vasculitis.
	Antiphospholipid syndrome	Associated with increased risk of venous and arterial thrombosis; anti-β2-glycoprotein-I antibodies probably convey independent stroke risk.
	Sjögren's syndrome	Rarely, complicated by cerebral vasculitis leading to headache, stroke, encephalopathy, and inflammatory CSF.
	Behçet's disease	Most commonly causes ICVT or relapsing encephalopathy with inflammatory CSF. Rarely associated with a vasculitis leading to ischaemic or haemorrhagic stroke.
	Relapsing polychondritis	Can be associated with an inflammatory vasculitis.
	Scleroderma	Infarction rarely reported due to vascular calcifications, vasoconstriction, and inflammatory vasculitis.
Inflammatory vasculopathies	Giant cell arteritis	Typically affects the extradural vertebral, petrous/ cavernous internal carotid, and ophthalmic and posterior ciliary arteries. Likely relates to the prominent external elastic lamina in the vessel wall, in contrast to the intradural segments.[33]
	Paraneoplastic vasculitis	Similar expression of antigens in arterial wall and occult malignancy; most commonly Hodgkin's lymphoma, leukaemia and lung cancer.
	Drug-induced vasculitis	Inflammatory systemic vasculitis most frequently associated with immunomodulators and antibiotics.
	Takayasu arteritis	Strokes due to low-flow from multiple cervicocephalic arterial occlusions, embolism, or ruptured flow-related aneurysms.
	Primary angiitis of the CNS	Inflammation of the small cerebral arteries and veins. Subcortical infarcts of varying ages in a minority.
	Susac's syndrome	Encephalopathy, branch retinal artery occlusions and hearing loss due to cochlear infarction.
	Cogan syndrome	Can mimic Susac's syndrome, but inflammatory infiltration of the cornea instead of retina. Stroke due to vasculitis rarely reported.
Non-inflammatory vasculopathies	Reversible cerebral vasoconstriction syndrome (RCVS)	Reversible, concentric narrowing and dilatation of medium-sized cerebral arteries. Triggers typically include cough and cold suppressants, selective

		serotonin reuptake inhibitors, triptans and chemotherapy.
	Moyamoya arteriopathy	Radiologically defined appearance of collateralisation due to severe stenosis or occlusion of distal ICA (see text).
	Posterior reversible encephalopathy syndrome (PRES)	Reversible cortico-subcortical vasogenic oedema (often parieto-occipital, but can also affect bilateral posterior watershed zones and cerebellum) can mimic stroke. Severe cases can develop infarcts due to vasospasm or thrombosis.
	Fibromuscular dysplasia	'String of beads' tubular segmental appearance in mid-to-high ICA and V3 segment of vertebral arteries. Can result in abnormal cervical vascular loops, stenosis/ occlusion, aneurysm and dissection.
	Connective tissue disorders	Marfan syndrome, Ehlers-Danlos syndrome type 4, osteogenesis imperfecta: arterial dissection.
	Radiation-induced vasculopathy	Cervico-cranial radiotherapy is associated with accelerated atherosclerosis, moyamoya angiopathy, cerebral microhaemorrhages and cavernomas. SMART is a late complication of cranial radiotherapy.
Infections	Bacterial	Particularly meningococcal/ pneumococcal meningitis, pharyngitis/ tonsillitis, M. tuberculosis, mycoplasma (meningitis, vasculitis), bartonella, syphilis, infective endocarditis.
	Viral	Particularly HIV, CMV and HCV, and more recently COVID-19. VZV can develop months after HSV infection (shingles, zoster ophthalmicus) leading to arterial stenosis and occlusion and an encephalopathy with multiple infarcts. CSF VZV DNA or anti-VZV IgG antibodies are diagnostic.
	Fungal	Particularly cryptococcus, candida, aspergillus and mucormycosis. Mechanisms include small vessel arteritis/ vasculopathy and fungal endocarditis.
	Parasitic	Particularly worms, neurotrichinosis, trypanosoma cruzi, malaria and cysticercosis. Various mechanisms including small vessel vasculitis, direct cystic compression of arteries, cardioembolism (Chagas disease), small vessel occlusion by infected erythrocytes (malaria).
	Spirochetal	Particularly leptospirosis and B. burgdorferi (Lyme). Mechanism is thought to be infectious vasculitis.
Haematological disorders	Hereditary coagulation disorders/ thrombophilia	Antithrombin III deficiency, protein C and S deficiency – leading to venous thromboembolism and paradoxical embolism via patent foramen ovale.

	Severe anaemia	Possibly due to thrombocytopaenia.
	Sickle-cell disease	Vessel occlusion due to rigid erythrocytes and their interaction with coagulation system and endothelium.
	Paroxysmal nocturnal haemoglobinuria	Typically venous thrombosis but rarely associated with arterial stroke.
	Haematological malignancy	Particularly leukaemia, intravascular lymphoma and lymphomatoid granulomatosis.
	Essential thrombocytosis	Prothrombotic state affecting venous and arterial systems.
	Thrombotic thrombocytopaemic purpura (TTP) and haemolytic uraemic syndrome (HUS)	Platelet microthrombi formation can cause cerebral infarcts or a PRES appearance.
	Paraproteinaemia	Hyperviscosity syndrome due to precipitation of abnormal plasma proteins: Waldenstrom macroglobulinaemia, multiple myeloma, POEMS.
	Disseminated intravascular coagulation (DIC)	In the context of sepsis, malignancy, trauma, obstetric complications or intravascular haemolysis
	Polycythaemia	Polycythaemia rubra vera, relative polycythaemia, secondary polycythaemia.
Drugs	Drugs of abuse	Particularly those with sympathomimetic effects such as heroin, cocaine, amphetamines and khat (chewed betel leaves): hypertension, vasoconstriction, impaired myocardial contractility and arrhythmia, prothrombotic states.
	Antipsychotic medications in elderly patients with dementia	Risperidone and olanzapine. Potential mechanisms include increased metabolic risk and dehydration due to sedation leading to thrombosis and orthostasis.
	Prothrombotic drugs	Various mechanisms, e.g. combined oral contraceptive pill, intravenous immunoglobulin, anabolic steroids, heparin (e.g. HIT due to PF4 antibodies including association with COVID-19 vaccine).
Malignancy	Malignancy-related coagulopathy or hyperviscosity syndrome	Venous and arterial thrombosis. More common with gastrointestinal malignancy (e.g. pancreas, stomach)
	Direct tumour effects	Arterial invasion/ compression, leptomeningeal metastases, tumour emboli, intravascular lymphomatosis.
	Marantic endocarditis	Immune-mediated damage to cardiac valves leads to sterile vegetations and cardioembolism. Most commonly associated with adenocarcinoma.
	Chemotherapy treatment	Activation of the coagulation pathway, vasospasm and endothelial damage. Intrathecal methotrexate-induced toxic leukoencephalopathy as a stroke

		mimic.
Genetic and metabolic diseases	X-linked	Fabry disease (GLA gene)
	Autosomal dominant	CADASIL (Notch3 gene), CARASAL (CTSA gene), RVCL (TREX1 gene), COL4A1.
	Autosomal recessive	Tangier disease (ABCA1 gene), CARASIL (HTRA1 gene), homocystinuria (most commonly CBS gene), Sneddon syndrome/ ADA2 deficiency (CECR1 gene)
	Mitochondrial	MELAS (pathology more likely to be cerebral oxidative metabolic derangement rather than true ischaemia) (may overlap with Kearns Sayre Syndrome - progressive external ophthalmoplegia, retinitis pigmentosa and cardiac conduction abnormalities)
Miscellaneous	Hereditary haemorrhagic telangectasia	Paradoxical embolism by pulmonary AVM
	Dissection (aortic and cervical arteries)	Mechanisms include occlusion of the great vessels, aneurysm formation and embolism or hypotension. Abdominal aortic dissections may occlude radicular arteries (e.g. artery of Adamkiewicz) leading to a mid-thoracic anterior spinal artery infarction. Consider connective tissue disorders, eg Marfan, Ehlers-Danlos type 4 and Loeys-Dietz syndromes
	Migrainous infarction	Persistent symptoms of migraine aura occurring in association with an ischaemic brain lesion; usually posterior circulation events in young females.
	Toxic effects of venom	Particularly scorpions, snakes and spiders
	Uncommon emboli	For example, intracranial aneurysms, fibrocartilaginous (intervertebral disc), cholesterol, air, fat.
	Post-procedure	Catheter angiography

CNS= central nervous system; CSF= cerebrospinal fluid; ICVT= intracranial venous thrombosis; ICA= internal carotid artery; SMART= stroke-like migraine attacks after radiotherapy; HIV= human immunodeficiency virus; HZV= herpes zoster virus; CMV= cytomegalovirus; HCV= hepatitis C virus; VZV= varicella vasculopathy; PRES= posterior reversible encephalopathy syndrome; HIT= heparin-induced thrombocytopaenia; PF4= platelet factor 4; GLA= α-galactosidase A gene; CADASIL= cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CARASIL= cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy; HTRA1= high-temperature requirement A serine peptidase 1*; CBS= cystathionine beta-synthase; ADA2= adenosine deaminase 2; CECR1= Cat Eye Syndrome Chromosome Region 1; CARASAL= cathepsin-A-related arteriopathy with* strokes *and leukoencephalopathy; CTSA= cathepsin-A; RVCL= retinal vasculopathy with cerebral leukodystrophy; TREX1= three prime repair exonuclease 1; COL4A1= collagen type 4 alpha 1; ABCA1= ATP-binding cassette transporter A1; MELAS= mitochondrial encephalopathy, lactic acidosis and stroke-like episodes*

Table 2 *– Key examination findings in rare causes of ischaemic stroke categorised by disease process*

Disease process	Examination findings	Example condition
Infection	Cardiac murmur, Osler nodes, Roth spots, Janeway lesions, splinter haemorrhages, intravenous injection sites, poor dental hygiene	Subacute bacterial endocarditis
	Skin or mucous membrane gumma	Tertiary syphilis*
	Dermatomal vesicular rash	Varicella zoster virus
	Liver failure - jaundice, palmar erythema, finger clubbing, spider angiomata	Chronic hepatitis C infection
	Erythema migrans, regional lymphadenopathy, myalgia, pharyngitis, conjunctivitis, periorbital oedema	Lyme disease
	Fever, oral thrush, lymphadenopathy, hepatosplenomegaly, seborrheic dermatitis, Kaposi's sarcoma	HIV
	Cachexia, fever, upper lung zone rales, pallor, lymphadenopathy, haemoptysis	Tuberculosis
	Inoculation site rash (skin creases, interdigital spaces, scalp), conjunctivitis, lymphadenopathy, fever, neuroretinitis, papillitis, Parinaud oculoglandular syndrome, encephalopathy	Bartonella
	Fever, conjunctivitis, splenomegaly, pharyngitis, lymphadenopathy (Weil's disease -jaundice and renal failure)	Leptospirosis
Autoimmune/ inflammatory vasculopathy	Livedo reticularis	APLS, CECR1 gene mutations (Sneddon syndrome, ADA2 deficiency)
	Oral and genital ulceration, uveitis, retinal vasculitis	Behçet's disease
	Photosensitive malar rash, discoid lupus, nail fold telangiectasia, Raynaud's phenomenon, calcinosis cutis	SLE
	Sensorineural hearing loss, yellow non-refractile retinal arterial wall plaques (Gass plaques)	Susac's syndrome
	Auricular chondritis, nasal chondritis (saddle nose deformity), ocular inflammation, sensorineural hearing loss	Relapsing polychondritis
	Asymmetrical absence of peripheral pulses and retinal neovascularization	Takayasu arteritis
Coagulopathy	Purpura	TTP, paraproteinaema, DIC, PRV
	Telangectasia	HHT
Genetic/ metabolic	Yellow papules in flexor areas, elastic skin, retinal angioid streaks	Pseudoxanthoma elasticum (premature atherosclerosis)
	Corneal opacities, angiokeratoma, posterior circulation event	Fabry disease
	Joint hypermobility, lens subluxation, translucent skin, inguinal hernia, abnormal uvula, scoliosis, arachnodactyly	Connective tissue disorders, such as Marfan, Ehlers-Danlos and Loeys-Dietz syndromes

	Marfanoid habitus, high myopia, dislocated lenses, osteoporosis, intellectual disability	Homocystinuria
	Sensorineural hearing loss, diabetes, retinitis pigmentosa	Mitochondrial disorders

*Neurosyphilis most commonly features in tertiary syphilis, but can occur at any stage, so examination for the painless chancre of primary syphilis or condyloma latum and palmoplantar rash of secondary syphilis may also be of diagnostic benefit.

HIV= human immunodeficiency virus; ALPS= antiphospholipid syndrome; ADA2= adenosine deaminase 2; CECR1= Cat Eye Syndrome Chromosome Region 1; SLE= systemic lupus erythematosus; TTP= thrombotic thrombocytopaenic purpura; DIC= disseminated intravascular coagulation; PRV= polycythaemia rubra vera; HHT= hereditary haemorrhagic telangiectasia.

Table 3 *– Investigations to consider in diagnosing uncommon causes of ischaemic stroke*

Modality		First line	Second line	Notes
Laboratory	Autoimmune screen	ANA, anti-Ro/SSA & anti-La/SSB antibodies, anti-dsDNA antibodies, ANCA, urinalysis (urine protein-to-creatinine ratio), serum protein electrophoresis, C3/ C4 complement levels, antiphospholipid antibodies	Pathergy test	Antiphospholipid antibodies include: lupus anticoagulant, IgG and IgM anticardiolipin antibodies and IgG and IgM anti-beta-2-glycoprotein.
	Infection screen	Serology for HIV, VDRL, hepatitis C virus, varicella zoster virus.	B. burgdorferi, Tuberculosis IGRA.	Varicella particular if vasculopathy on angiography
	Thrombophilia screen	*Arterial thrombosis:* antiphospholipid antibodies, primary VITT screen (platelet count, D-dimer, fibrinogen) *Venous thrombosis:* factor V Leiden, prothrombin G20210A mutation, protein C&S*, antithrombin III deficiency*	Serum homocysteine level, secondary VITT screen (anti-PF4 antibodies and functional heparin-induced thrombocytopaenia testing)	Thrombophilia screen is most useful when it would change management (e.g. no other reason for life-long anticoagulation such as recurrent VTE).
	Urine toxicology screen	Cocaine, amphetamines		Often prompted by history and though otherwise rare, usually tested for early in presentation due to loss of sensitivity with delayed testing.
	Cerebrospinal fluid		Opening pressure, microscopy and culture, white and red cell count, glucose, protein, oligoclonal bands, lactate, viral PCR, cytology, flow cytometry, save sample	CSF most useful in possible infective, inflammatory or malignant causes of vasculitis. Opening pressure useful if considering raised intracranial pressure (e.g. CVT).
	Genetic and metabolic		Single gene and metabolic testing (see *Table 1*), mitochondrial genome sequencing	
Imaging	Brain parenchymal imaging	Contrast-enhanced MRI brain, including gradient echo/ susceptibility-weighted imaging sequences		Identification of blood-brain barrier disruption/ meningeal based disease due to an active infective, inflammatory

				or malignant process. Subarachnoid haemosiderin deposition can be seen in amyloid angiopathy, RCVS/ vasculitis.
	Angiography	CT/ MR angiography aortic arch to vertex	CT angiogram aortic arch and aorta	Identification of aortic atherosclerosis, aortic dissection, or aortitis (depending on history and inflammatory markers).
			Digital subtraction angiography (DSA)	Gold-standard angiography and flow dynamics, diagnosis and treatment of vascular malformations
			High resolution intracranial vessel wall imaging	High-resolution views of intracranial atherosclerotic plaque, mural haemorrhage (dissection), aneurysms and presence or absence of wall enhancement.
			Fluorescein angiography	To investigate for retinal vasculitis
	Body imaging	CT chest, abdomen and pelvis	Positron emission tomography (PET)	Investigation for extracranial malignancy or infective abscess/ collection
Procedures	Cardiac	Transthoracic echocardiogram	Transoesophageal echocardiogram	Detection of patent foramen ovale, size of shunt and associated atrial septal aneurysm. Also detection of vegetations, myxoma and congenital heart defects.
	Biopsy		Brain and/ or meningeal, extra-cranial sites identified on body CT or PET	CNS vasculitis or malignant/ infective extracranial tissue detected on CT/ PET. Brain biopsy is invasive and has a variable yield (50-70%).[34]

*cannot test with concurrent anticoagulation therapy.

ANA= antinuclear antibody; SSA/ SSB= Sjogren syndrome antigen A/ B; ANCA= anti-neutrophil cytoplasmic antibody; IGRA= interferon-gamma release assay (e.g. QuantiFERON); VITT= vaccine-induced immune thrombotic thrombocytopaenia; PCR= polymerase chain reaction; VDRL= venereal disease research laboratory; CT= computed tomography; PET= positron emission tomography.

Box 1 - Cancer-related ischaemic stroke

Illustrative case

A 54-year-old woman presented with a complete left MCA syndrome 4 hours from witnessed onset. On examination her blood pressure was 143/ 64mmHg, pulse 84 and regular, normal heart sounds and temperature 36.5 degrees. She had dense right-sided weakness, neglect and mixed aphasia; National Institute of Health Stroke Scale (NIHSS) was 17. Non-contrast CT brain scan excluded intracranial haemorrhage and CT angiogram demonstrated a proximal left middle cerebral artery thrombus. She underwent intravenous thrombolysis and subsequent successful mechanical thrombectomy within 6 hours; her NIHSS at 24 hours later was 5.

Further history from the patient's partner revealed she was awaiting urgent assessment for a 3-month history of unintentional weight loss and dyspnoea. Of note, she was a current smoker with a 40-pack-year history. She had an erythrocyte sedimentation rate (ESR) of 86mm/h. MRI brain showed multi-territory small, non-enhancing, acute infarcts. A transthoracic echocardiogram found no valve vegetations, ventricular thrombus or patent foramen ovale. A chest radiograph demonstrated a soft-tissue density in the right upper lung zone concerning for malignancy. An urgent staging CT revealed a likely lung primary malignancy with liver and bone metastases.

Discussion

Thrombosis is a major cause of death in patients with cancer; arterial thrombosis causing stroke and TIA is less common than venous thromboembolism (VTE), but is well documented.[35] In one large meta-analysis of population-based cohort studies, including 10.5 million patients, there was a two-thirds higher risk of stroke compared to cancer-free controls, particularly in the young, females and in those with pancreatic, head and neck, lung, and hematologic malignancies.[36]

Cancer-related stroke should be suspected when more common causes have been excluded, particularly in patients with unexplained weight loss, pyrexia of unknown origin, night sweats or a prior history of malignancy; small, scattered multi-territory infarcts with normal cardiac rhythm and function; combined venous and arterial emboli in a short space of time; and elevated D-dimer or inflammatory markers.

Potential pathophysiological mechanisms include:

- Malignancy-related coagulopathy (due to the secretion of procoagulant molecules or platelet activation) with paradoxical venous embolism through a PFO or arterial embolism to the brain;
- Direct invasion of cancer or metastases into cerebral or cervical vasculature;
- Paraneoplastic vasculitis;
- Treatment-related effects: radiation-induced vasculopathy, chemotherapy*, immunosuppression with opportunistic infection and meningoencephalitis;
- Other: cardiac tumours (atrial myxoma, fibroelastoma, aortic sarcoma), tumour embolism, hyperviscosity syndrome and disseminated intravascular coagulation.

There is no strong evidence to guide the management of cancer-related ischemic stroke, in contrast to the use of low-molecular-weight heparin in the treatment of cancer-related VTE which has been shown as superior to warfarin in several randomised trials.[37]

**Chemotherapy can lead to activation of the coagulation pathway, endothelial damage and/ or vasospasm. L-asparaginase, bevacizumab, cisplatin, doxorubicin and tamoxifen have all been associated with an increased risk of ischaemic stroke.*

Ischaemic stroke in a patient with HIV

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Focused history and examination

- HIV-related risk factors – conventional vascular risk factors, illicit drug use, shingles, tuberculosis exposure and use of combined antiretroviral therapy
- Indicative mechanism -
  - Cerebral vasculitis - headache, seizures or encephalopathy
  - Opportunistic CNS infection – features of M. tuberculosis meningovasculitis, VZV vasculopathy, neurosyphilis (*Table 1*)
  - Cardioembolism – fever, cardiac murmur, multifocal, deficits
  - Accelerated atherosclerosis – comorbid peripheral vascular or cardiac disease, cardiac bruit.

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Specific investigations

- MRI/ MRA brain (+/- contrast): multi-territorial infarcts, cerebral small vessel disease, CNS vasculopathy
- Laboratory investigations: CD4 count and HIV viral load, treponemal (immunoassay and agglutination test) and nontreponemal tests, viral hepatitis B and C serology, blood cultures (pyrexial or raised inflammatory markers), VZV IgG
- Chest radiograph: infection (TB), tumours (lymphoma), cardiac disease, vasculopathies
- Lumbar puncture (if no clear evidence of alternative cause, e.g. cardioembolic): microscopy and culture; protein and glucose concentration; viral PCR; acid-fast bacilli; VDRL/RPR (if syphilis blood screen positive); if CD4+ count <200 cells/mm or inflammatory CSF- India ink microscopy/ cryptococcal antigen, toxoplasmosis serology

Box 2 - *Approach to ischaemic stroke in a patient with HIV*

HIV-associated ischaemic stroke

- HIV infection is thought to increase the risk ischaemic stroke by a number of potential mechanisms, including HIV-vasculopathy, cardioembolism, opportunistic infection and atherogenic combined anti-retroviral therapy (cART).
- Conventional vascular risk factors and mechanisms remain the most common cause of ischaemic stroke in patients with HIV, particularly with improving life expectancies. Protease inhibitors are associated with metabolic complications, including dyslipidaemia, insulin resistance and diabetes.
- HIV-vasculopathy refers to any extra- or intracranial arterial abnormality caused directly or indirectly by HIV, but excluding vasculitis due to opportunistic infection. This includes aneurysm formation, small vessel disease, cerebral vasculitis and accelerated large-vessel atherosclerosis (associated with low-grade chronic systemic inflammation and cART).
- The most frequent opportunistic infections that cause stroke in patients with HIV include tuberculous meningitis, varicella zoster virus vasculitis and meningovascular syphilis.
- There is no evidence to suggest that acute and secondary prevention management of ischaemic stroke differs in any way to patients without HIV.
- Patients receiving cART, particularly protease inhibitors, should have proactive vascular risk factor management due to metabolic derangements.

PACNS	RCVS	Atherosclerosis
Older men	Young to middle aged women	Older patients (particularly Asian and black) with vascular risk factors
Subacute headache, focal neurological deficit and seizures at presentation	Recurrent thunderclap headache	Isolated focal neurological deficit
Fulminant course and poor prognosis without immunosuppressive therapy	Often benign, self-limiting course with supportive care	Acute, non-progressive event
CSF usually abnormal (protein >100 mg/dL and 5–10 cells/mm)	CSF normal or mildly abnormal	CSF normal
Multifocal infarcts of varying age at presentation	Parenchymal imaging usually unremarkable at presentation but can develop ischaemic stroke and cortical subarachnoid haemorrhage	Acute infarct distal to a stenosed artery

Box 3: Distinguishing causes of intracranial arterial stenosis: primary angiitis of the CNS (PACNS), reversible vasoconstriction syndrome (RCVS) and atherosclerosis

Competing interests
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RH, DJW and MP conceived the concept. RH wrote the first draft. RS provided expert neuroradiology input. Other authors reviewed and critically appraised the manuscript.

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