Cryptogenic stroke

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ABSTRACT

Although in the last few years emerging conventional and unconventional radiological and laboratory techniques have shed light on different pathophysiologic causes of stroke, nowadays almost 25% of ischemic strokes results of undetermined etiology. Different diagnostic criteria have been developed to define cryptogenic stroke and to establish its prevalence in stroke units. Different studies tried to unravel mechanisms of cryptogenic stroke and to evaluate adequate primary and secondary preventive measures, but standardized diagnostic and therapeutic strategies are still missing. In this review we report the most relevant updated notions in cryptogenic stroke providing an overview of the definition, the recommendations for diagnostic evaluation and the updated treatment strategies for secondary prevention.

Introduction

According to a recent study, in 2010 stroke represents the second cause of death and the third cause of reduced disability-adjusted life-years worldwide,[1] being a leading cause of adult disability in Western countries.[2,3] Ischemic stroke may be due to small vessel occlusion, large artery atherosclerosis, cardioembolism, or other less common causes (*e.g.*, dissection, hypercoagulable disorders, vasospasm, drug abuse). It is noteworthy that some conditions (*e.g.*, hematocrit levels) may act as risk factors for ischemic stroke, facilitating its occurrence and influencing its prognosis.[4,5] Each type of stroke has different risks of recurrence, prognosis, and treatment. Residual disability after a stroke may vary largely, depending on the stroke subtype, being often severe in subarachnoid hemorrhages[6] and in stroke of undetermined origin. In fact, even after a comprehensive investigation, a third of ischemic strokes result of undetermined cause, and consequently they are named cryptogenic stroke (CS).[7-11]

At the moment, there are no standardized diagnostic criteria to reliably and consistently define a stroke as CS. In the past most studies concerning CS were hospital based with study designs characterized by differences in the criteria of classification, characteristics and susceptibility of the studied population and extent of diagnostic assessment.

Timely diagnosis and control of cardiovascular risk factors are a priority for adequate primary and secondary prevention of stroke. Although different studies have extensively investigated various underlying pathologies in patient with stroke, at the moment no randomized trials concerning CS have established an optimal secondary prevention strategy.[12] Because of the lack of available evidence, there is an urgent need for a standardized approach to diagnose and manage patients with CS in order to guide clinical practice and future research. The aim of this review is to introduce the most relevant updates on CS and to provide an overview concerning the definition, the recommendations for diagnostic evaluation, and the treatment strategies for secondary prevention in CS and in silent stroke.

Definition

In CS the concept of undetermined etiology represents a key word to define the unknown causative fac-

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tors and to define a consequently correct therapeutic approach.

At least three classifications try to define the cryptogenic nature of an acute stroke: i) the Trial of Org 10172 in Acute Stroke Treatment Criteria (TOAST); ii) the Causative Classification of Stroke System (CCS); and iii) the Atherosclerosis, Small vessel disease, Cardiac causes, and Other (ASCO) uncommon causes system.

The TOAST classification is the most widely used classification system. Nevertheless, it is universally considered to overestimate the frequency of CS.[13] TOAST criteria define CS as a brain infarct not attributed to a definite source of large-vessel atherosclerosis, cardioembolism, or small vessel disease after completing an extensive cardiac, vascular, hematologic, and serologic investigation; or if the evaluation has been incomplete; or in the presence of multiple competing causes (unclassified) with either probable evidence for each or improbable evidence for a single cause. Definite criteria also indicate when the nature of the event seems to be embolic but the source of embolism remains undetermined. That happens in the presence of: i) angiographic evidence of abrupt cutoff consistent with a blood clot within otherwise normal intracranial arteries; or ii) angiographic imaging showing complete recanalization of a previously occluded artery; or iii) presence of multiple acute infarctions that have occurred closely related in time without detectable abnormalities in the relevant vessels.[14,15] Practically, on the basis of the TOAST classification, the number of strokes of unknown etiology represent approximately 40% of all strokes, including cases with potential multiple etiologies or with incomplete diagnostic work-up. Moreover, the definition of some subtypes relies only on the users' opinion or interpretation. As a result, the TOAST classification system only has moderate inter-rater reliability,[16-18] while the over-classification of many patients into the undetermined category may lead in some instances to consider personal opinion and guessing rather than the published TOAST criteria.[19]

The CCS project is a web-based classification system based on TOAST, which categorizes ischemic stroke into potentially five major subtypes (supra-aortic large artery atherosclerosis, cardio-aortic embolism, small artery occlusion, other causes, undetermined causes). It classifies stroke based on published evidence, and by integrating the results of multiple diagnostic stroke evaluation procedures [diffusion-weighted magnetic resonance imaging (DW-MRI), computed tomography angiography (CTA) and MR angiography (MRA), echocardiography (both transthoracic and transesophageal), and electrocardiogram (ECG)-Holter monitoring]. If multiple potential causes existed CCS assigns the patient to a subtype choosing the most likely mechanism.[20] According to CCS system classification, a CS should be identified as *cryptogenic embolism* and *other cryptogenic*. Cryptogenic embolism is identified when there is *angiographic evidence of abrupt cut-off consistent with a blood clot within otherwise angiographically normal looking intracranial arteries, imaging evidence of complete recanalization of previously occluded artery, or the presence of multiple acute infarctions that have occurred closely related in time without detectable abnormality in the relevant vessels*. Clinical forms not fulfilling the criteria for cryptogenic embolisms are identified as *other cryptogenic*.[20-22]

ASCO is a phenotypic stroke classification system proposed by an international group of leading stroke experts.[23] It assigns a level of likelihood to each potential cause and reflects the most likely etiology considering also other unrelated vascular conditions.[24] This system does not appear useful for diagnosis of CS since it classifies ischemic strokes into 625 phenotypic subtypes, it integrates features unrelated to the event into stroke subtype assignments, and it relies on the availability of brain and vascular imaging studies. It can assist further researches in strokes classified by TOAST as undetermined.

A characteristic neuroimaging feature of CS is represented by the presence of single or multiple territorial infarcts, suggestive of embolism and identifiable in more than 60% of patients with CS.[25] Moreover, about 65% of patients with an infarct of undetermined origin reported in NINCDS Stroke Databank were found to have less well-documented sources of embolism on further evaluation.[26]

Recently, the term *embolic stroke of undetermined source* (ESUS) has been introduced to identify patients with non-lacunar stroke in whom there is no evidence of intra- or extra-cranial stenosis >50% nor relevant source of cardiac embolism (*i.e.*, atrial fibrillation), nor other specific mechanisms of stroke.[12] ESUS could be attributed to paroxysmal atrial fibrillation, cancer associated to patent foramen ovale (PFO) or pulmonary fistula, minor cardiogenic embolic conditions or atheroembolism and it likely represents a new frontier in the development of a clinical and therapeutic approach for cryptogenic stroke evaluation.

Excluding established causes of ischemic strokes

The causes of ischemic stroke are heterogeneous and sometime relatively uncommon. Inappropriate diagnostic testing may lead to erroneously consider a stroke as CS. In some instances, an etiopathological diagnosis can be obtained in the follow-up and/or after repetition of exams. Rigid classification systems with arbitrary cut-offs (such as the ≥50% criterion for relevant carotid stenosis) may lead to consider a stroke cryptogenic. That is because an artery with mild degree

stenosis can harbor an unstable plaque responsible of artery-to-artery embolism. When the initial ischemic stroke work-up (brain neuroimaging, noninvasive extracranial and intra-cranial vessel imaging, and cardiac monitoring for at least 24 h)[27] is insufficient for a defined etiology, additional tests may help to achieve the stroke etiology. Possible causes of ischemic stroke are plenty and choosing among all the possible diagnostic is challenging. Although extensive pathogenic workup generally increases diagnostic accuracy, it may also discover bystander conditions not necessarily relevant to the stroke event (*e.g.*, PFO). Some features, symptoms, and signs and the accurate interpretation of results may suggest specific stroke etiologies and guide further appropriate diagnostic testing.

In CS with a potentially cardioembolic infarct pattern on neuroimaging, advanced cardiac testing should be performed. Identification of occult atrial fibrillation is important because of treatment implications. While standard 12-lead ECG and inpatient telemetry are useful in detecting chronic or frequent paroxysmal atrial fibrillation, they may not be sufficient to detect infrequent paroxysmal AF not-associated with cardiac symptoms. In those cases, advanced cardiac rhythm monitoring may yield benefits.[28,29]

Transthoracic echocardiography is the preferred tool for cardiac imaging but in patients with stroke it can often be inadequate or insufficient. A transthoracic echocardiography may oversee many conditions including aortic arch atheroma, left atrial appendage thrombus, left atrial or left ventricular thrombus, endocarditis, PFO, cardiac mixoma.[30] In those cases, transesophageal echocardiography adds diagnostic accuracy. In selected patients coronary CTA may add further diagnostic accuracy to the detection of cardiac or aortogenic embolic sources.[31,32]

An history of recent minor trauma, sudden neck movements (*e.g.*, chiropractic neck manipulation) or prolonged abnormal neck posture associated with headache or neck pain at stroke onset can suggest an arterial dissection.[33] A painful Horner syndrome, or coexisting cranial neuropathies, may also rise suspicion for dissection. In the recognition of an arterial dissection a frequent mistake is the inappropriate or delayed investigation. Ultrasonography, CT or MRA are the standard techniques for diagnosing a dissection but each of them can mistakenly result normal because of the location of the dissection, of a superimposed thrombus formation, and of a recanalization. MR with axial T1-weighted fat-suppressed images may be useful to show the presence of intramural hematoma.

In selected cases, other less common conditions may be considered as rare mechanisms of stroke. Illicit drug abuse (*e.g.*, cocaine, amphetamines, ecstasy, phencyclidine; therapeutic drugs-L-asparaginase, cytosine arabinoside) can cause ischemic stroke; toxicologic studies are often productive, even when drug use is not reported by the patient.

A number of monogenic diseases can cause stroke and should be considered in the appropriate clinical setting. Family history and associated features may be relevant to raise the suspicion and to perform a specific test. Table 1 reports features of genetic diseases and specific diagnostic testing. Vasculitides are other uncommon possible causes of ischemic stroke. With the only exception of the central nervous system primary angiitis, which exclusively involves the central nervous system, all other vasculitides are associated with systemic involvement. Clinical features and diagnostic testing for primary vasculitides are reported in Table 2. Collagen vascular disease may also be associated with secondary immune-complex-related cerebral vasculitides; those conditions include systemic lupus erythematosus, rheumatoid arthritis and Sjögren's syndrome. Laboratory exams that should be performed in the clinical suspect of vasculitides are reported by Berlit.[34]

Pro coagulant states may represent possible causes of ischemic stroke, too. Antiphospholipid antibody syndrome is a pro thrombotic disorder that can affect venous and arterial circulation.[35] Serum testing for acquired antiphospholipid syndrome may be considered in the presence of a history of prior venous thromboembolism, second trimester abortion, or rheumatologic disorder. The diagnosis requires the persistence of high titers of autoantibodies of the IgG or IgM isotype (for >12 weeks), detected by enzyme-linked immunosorbent assay for anti-β2-glycoprotein I or anticardiolipin antibodies or by lupus-anticoagulant assays. Other conditions that can also be associated with an acquired hypercoagulable state include pregnancy, hormonal contraceptive use, exposure to hormonal treatments such as anabolic steroids or erythropoietin, nephritic syndrome, and cancer. Patients with cancer may have distinctive D-dimer levels (a marker of coagulopathy, >20 × higher than those without cancer) and infarct patterns (multiple lesions in multiple vascular territories).[36] Positron emission CT may help in detecting occult malignancies.

An ischemic stroke may be due also to inherited thrombophilia. Tests for thrombophilia have high costs and low diagnostic accuracy. Their results can fluctuate, and repeated assessment is needed or genetic testing should be done where possible. Clues for a hypercoagulable state include a history of deep venous thrombosis or multiple miscarriages. Factors to be tested are reported by Berlit.[34]

In immunosuppressed patients or in those with high exposure risk and in patients with evidence of multifocal infarcts, an infectious etiology such as virus infections (varicella-zoster virus, herpes simplex virus, cytomegalovirus, HIV), syphilis, and tuberculosis should be considered and confirmed by serum and if necessary by cerebrospinal fluid examination.

Table 1. Most common monogenic diseases, which have ischemic stroke as one of their possible presenting feature.

Disease	Mutation	Hereditary	Onset	Clinical features	Ischemic stroke mechanisms	Diagnostic testing
Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)	*NOTCH3* gene on chromosome 19p13.1-13.2 *HTRA1* gene on chromosome 10q26.13	Autosomal dominant	Early adulthood	Subcortical vascular dementia, depression and other psychiatric disorders, migraine with aura, and recurrent strokes. Temporal pole white matter hyperintensities at brain MRI; external capsule and corpus callosum frequently involved	Small vessel disease	Skin biopsy (granular osmiophilic material at electron microscope) and genetic testing
Cerebral autosomal recessive arteriopathy with subcortical infarcts and leucoencephalopathy (CARASIL)	*COL4A1* on chromosome 13q34	Autosomal recessive	Early adulthood	Spondylosis, low back pain, diffuse baldness, gait disturbance with spasticity, dementia	Small vessel disease	Genetic testing
COL4A1		Autosomal dominat	Variable	Infantile hemiparesis, seizures, migraine, visual loss, dystonia, ischemic and hemorrhagic strokes, mental retardation, dementia, eye defects (retinal arterial tortuosity, Axenfeld-Rieger anomaly, cataract), kidney involvement, muscle cramps, Raynaud's phenomenon, cardiac arrhythmia at brain MRI, diffuse leukoencephalopathy, subcortical infarcts, microbleeds, porencephaly, cerebral aneurysms	Small vessel disease	Genetic testing
Ehlers-Danlos type IV	Collagen type III on chromosome 2q31	Autosomal dominant	Childhood	Characteristic facial appearance, thin and translucent skin that bruises easily, and fragile arteries and intestines that are prone to rupture	Arterial dissection	Genetic testing
Fabry disease	*GLA* gene on chromosome Xq22 (deficiency of enzyme α-galactosidase A)	X-linked recessive	Adulthood	Skin (angiokeratoma), eye (subcapsular cataract, cornea verticillata, tortuous vessels), central nervous system (stroke or TIA, epilepsy, white matter abnormalities, vertebrobasilar dolicoectasia), kidney disease (reduced creatinine clearance and proteinuria), peripheral nerves (acroparesthesia and impaired sweating), cardiac (cardiac arrhythmias, hypertrophic cardiopathy), ear (hypoacusia, tinnitus), gastrointestinal (pain)	Small and large vessel disease	Men: deficit in serum α -galactosidase Women: genetic testing

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Table 1. Continued from previous page.

Disease	Mutation	Hereditary	Onset	Clinical features	Ischemic stroke mechanisms	Diagnostic testing
Hereditary endotheliopathy with retinopathy, nephropathy, and stroke (HERNS)	*TREX1* gene mutation on chromosome 3p21.31	Autosomal dominant	Adulthood	Visual disturbances (vascular retinopathy), stroke-like episodes, dementia, kidney disease, contrast-enhanced white matter lesions at brain MRI	Small vessel disease	Genetic testing
Homocystinuria	21q22.3 and others (cystathione b-synthase and others)	Autosomal recessive	Childhood	Mental retardation, ectopia lentis, skeletal deformities and thromboembolic events	Large and small vessel disease, cardioembolism, arterial dissection	Very high homocysteine (>100 µmol/L); urine amino acid analysis and elevated plasma methionine
Marfan syndrome	15q21.1 (fibrillin 1)	Autosomal dominant	Childhood	Tall stature, joint hypermobility, ectopia lentis, retinal arteriolar irregularities, mitral and aortic incompetence, arterial dissection	Cardioembolism and arterial dissection	Clinical, genetic testing
Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS)	Mitochondrial; A3243G and T3271C in tRNA Leu	Maternal	Variable	Seizures, lactic acidosis, stroke-like episodes, migrainous headaches, cognitive impairment, hearing loss, muscle weakness, exercise intolerance, eyelid ptosis, short stature, pigmentary retinopathy, axonal multifocal neuropathy, sensorineural hearing loss, ophthalmoparesis, optic neuropathy, diabetes mellitus, hypertrophic cardiomyopathy and Wolff-Parkinson-White syndrome	Atypical	High lactate and piruvate, genetic testing, red ragged fibers at muscle biopsy
Moyamoya disease (familiar type)	3p24.2-p26, 6q25, 8q23, 12p12 and 17q25	Autosomal dominant with incomplete penetrance	Juvenile or adulthood	Ischemic and hemorrhagic stroke, seizures	Internal carotid stenosis with new vessel formation	Cerebral angiography
Pseudoxanthoma elasticum	*ABCC6* on chromosome 16p13.1	Autosomal recessive	Childhood	Yellow papules/plaques on the lateral neck or body, gastrointestinal disturbances, claudicatio, angina, stroke, visual disturbances (angioid streaks of the retina and Peau d'orange changes)	Calcification of the elastica media and intima of the blood vessels	Calcifications at skin biopsy, genetic testing
Sickle cell disease	Hemoglobin on chromosome 11p15.4	Autosomal recessive	Childhood	Vaso-occlusive crises (organ ischemia due to vessel occlusion; cause of strokes), hematological crises (sudden exacerbation of anemia; cause of strokes), and infectious crises (defective immunity due to dysfunctional spleen)	Large and small vessel disease, hemodynamic insufficiency	Hemoglobin electrophoresis (hemoglobin S), genetic testing; ultrasound to identify subjects at risk of stroke

MRI, magnetic resonance imaging; TIA, transient ischemic attack.

Moyamoya disease is an uncommon cause of ischemic stroke. The condition is characterized by progressive bilateral stenosis of the internal carotid arteries with compensatory formation of an abnormal network of perforating blood vessels providing collateral circulation.[37] The etiology and pathogenesis of Moyamoya disease remain unclear. There are inherited forms or it may be associated with head radiation, Down syndrome, neurofibromatosis type 1, sickle cell anemia and other less common conditions. The disease may be suggested by the presence, at conventional MRI, of flow void signals (resulting from basal collaterals) at the level of basal ganglia and thalami or by the presence of the ivy sign (linear high signal following a sulcal pattern at fluid attenuated inversion recovery sequences supposed to represent slow flow in poorly perfused cortical circulation), by bilateral stenosis at the apices of the internal carotid arteries at brain CT or MRA (even if unilateral findings may be present during the early course of the condition) and thereafter confirmed by the characteristic *puff of smoke* appearance of collateral vessels at brain angiography. More rare causes of ischemic stroke are represented by Sneddon syndrome characterized by livedo racemosa and stroke,[38] Susac's syndrome characterized by branch retinal artery occlusion, hearing loss, encephalopathy and stroke[39] and migrainous stroke.[40,41]

Embolic strokes of undetermined source

ESUS is a new clinical construct that has been recently proposed.[12] ESUS has been designed as a redefinition of CS which tries to move forward by prompting the execution of some ancillary diagnostic tests in order to exclude definite causes of cerebral infarction. The construct is based on the rationale that the underlying mechanism of CS is embolism. ESUS category mostly includes cases where exams show a source not definitely associated with an embolic potential.[12,13] However, by strictly applying ESUS work-up and diagnostic criteria also cases where exams do not show any possible source will fall in the ESUS category whereas stroke events with incomplete work-up or with two or more possible causes will remain CS.[12] The aim of this construct is to define a homogeneous group of patients with embolic stroke which could be included in clinical trials of secondary prevention.

Diagnostic criteria for ESUS as well as the minimum diagnostic assessment necessary for diagnosis are reported by Hart *et al*.[12] In brief, ESUS is a stroke, not lacunar referring to morphology of the lesion, not associated with extra or intracranial stenosis ≥50% in the arteries supplying the ischemic area, not associated with a cardioembolic source of embolism, and not associated with other specific causes of stroke (*e.g.*, dissection, genetic disease, vasculitis, thrombophilia).[12] The definition of a minimum set of diagnostic exams to ascertain stroke cause is a point of novelty with respect to previous definition of CS. The causes encompassed in the ESUS include emboli from cardiac origin (either from structural diseases or for covert atrial fibrillation), emboli originating from arteries (aortic plaques and non-stenotic plaques of extra and intracranial vessels), emboli originating from veins (paradoxical embolism), and emboli originating from tumors.[12,13] Most of the causes that TOAST criteria consider depending on minor-risk cardioembolic sources[13] fulfill ESUS criteria and can be considered as ESUS.[12,13]

According to data from a retrospective hospital-based study, ESUS represent 10% of all first-ever ischemic strokes and main causes are represented by covert atrial fibrillation, moderate systolic or diastolic left ventricular dysfunction, and cerebral artery non stenotic plaques.[42] At present, the ESUS clinical construct has not been validated by prospective studies and in this subgroup prognosis is not clearly defined yet. Some recent data showed that long-term mortality risk in ESUS is lower compared to cardioembolic strokes despite similar rates of recurrence and of composite cardiovascular end-point.[42] Recurrent stroke risk is higher in ESUS than in non-cardioembolic strokes. Moreover, the ESUS category includes heterogeneous conditions since patients are allocated to this group in the absence of a well-defined stroke cause and not in the presence of a specific cause (*e.g.*, cardioembolic in the presence of atrial fibrillation). This sort of negative definition might bias diagnosis since a patient lacking a definite cause at stroke onset may turn out, after a more extensive follow-up or with additional testing, to have a definite cause such as vasospam, *in situ* thrombosis with recanalization, vasculitides, hemodynamic mechanisms, transient hypercoagulable states.[43] According to the definition of ESUS, strokes with incomplete evaluation or caused by 2 or more causes will remain cryptogenic. Additionally, there are some features of cerebral embolism that are not requested for definition of ESUS but which may support, even if they are not specific, an embolic mechanism such as acute lesions in different vascular territories, a new acute infarct in a vascular territory with previous lesions in different vascular territories, and hemorrhagic transformation.

Silent strokes

A silent stroke is a particular instance of CS: a clinically silent and unexpected evidence of a vascular brain lesion of unknown origin. According to the American Heart Association/American Stroke Association (AHA/ASA)[44] it could be defined: *Imaging or neuropathological evidence of central nervous system infarction, without a history of acute neurological dysfunction attributable to the lesion*. Microbleeds, present in around 6% of healthy elderly subjects,[45] are

Table 2. Main primary vasculitides associated with ischemic stroke.

Disease	Vessel size and histologic feature	Clinical features	Stroke occurrence and pattern	Diagnosis
Behçet syndrome	Small-vessel, venous system	Recurrent oral ulcerations, recurrent genital ulceration, eye lesions (uveitis, cells in the vitreous on slit lamp examination or retinal vasculitis), skin lesions (erythema nodosum)	Not common; ischemic stroke or cerebral venous thrombosis	Positive pathergy test result (a skin lesion is produced with a sterile needle; if an erythematous papule develops as a sign of skin hyperreactivity within 48 h the test is positive); no pathognomonic laboratory or histologic findings exist
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)	Small-vessel, necritozing vasculitis	Allergic diathesis and asthma, renal, and lung involvement, polyneuropathies	Rare; ischemic and hemorrhagic stroke, subarachnoid hemorrhage	pANCA/MPO common
Giant cell arteritis	Large and medium vessels, granulomatous vasculitis	Age >60 years, fever, malaise, weight loss, polymyalgia rheumatica, new onset persisting headache, jaw claudication, tenderness of the temporal arteries, diplopia, flimmer scotoma, amaurosis fugax, blindness	Rare; posterior circulation preferentially involved	Raised ESR and CRP; dark halo at colour duplex sonography; vasculitis with mononucleated cell infiltrates and giant cells on a temporal artery biopsy
Polyarteritis nodosa	Medium-vessel, systemic necrotizing vasculitis	Fever, malaise, weight loss, arthritis, livedo reticularis, acral necroses, testicular pain, severe peripheral ischemia, myalgias, mononeuritis or polyneuritis, impaired renal function, hepatitis B or C virus antibodies	Not common; ischemic and hemorrhagic stroke, progressive encephalopathy	Combined biopsy of muscle and nerve demonstrating the necrotizing granulomatous inflammation; pathologic arteriographic findings
Primary central nervous system angiitis	Brain vessels	Headache, seizures, myelopathy and encephalopathy	Ischemic and hemorrhagic stroke	CSF pleocytosis and a protein elevation; angiography demonstrating bilateral vessel stenoses or occlusions; brain and leptomeningeal biopsy demonstrating angiitis
Takayasu arteritis	Large-vessels; granulomatous panarteritis of the aorta and its major branches	Age <50 years, arthralgia, fever, fatigue, headaches, rashes and weight loss, claudication of extremities, systolic blood pressure differences of more than 10 mmHg between both arms and decreased brachial artery pulse, bruit over subclavian arteries or abdominal aorta	Ischemic stroke	No specific laboratory abnormalities; MR or CT angiography, digital subtraction angiography showing narrowing or occlusion of the aorta, its primary branches or large arteries (not due to arteriosclerosis, fibromuscular dysplasia or similar causes)
Kawasaki disease	Medium-vessel	Young children, prolonged fever, diffuse mucosal inflammation, indurative edema of the hands and feet, a polymorphous skin rash, and non-suppurative lymph-adenopathy	Rare; ischemic stroke	Increased markers of inflammation; urine proteins meprin A and filamin C
Granulomatosis with polyangiitis (Wegener's)	Small-vessel, necrotizing granulomas	Necrotizing granulomas of the nose, paranasal sinuses, mouth and pharynx; non-septic meningitis, occlusive or communicating hydrocephalus, lung inphiltrates, nephritis, polyneuropathy	Not common; ischemic and hemorrhagic stroke, progressive encephalopathy	cANCA/present in many cases

pANCA/MPO, antineutrophil cytoplasmic/myeloperoxidase antibodies; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; CSF, cerebral spinal fluid; MR, magnetic resonance; CT, computed tomography.

a type of *silent cerebral hemorrhage* but they will not be considered here.

The development of the concept of silent cerebral infarction started from the recognition that ischemic injury can be identified pathologically in patients without a history of stroke or transient ischemic attack (TIA).[46] The neuroimaging added a new value in the appraisal of this pathological entity. Studies with CT indicated that a range from 10% to 38% of acute stroke patients had evidence of a vascular lesion without any history of prior stroke.[47,48] In patients with silent lesion coexisting with a clinically manifest stroke, the same proportion of clinical stroke subtypes was found.[49] In studies with MRI the prevalence of silent strokes varied from 8% to 28%,[50] depending on the age of the population. Furthermore, a gender difference turned out in epidemiological studies on silent infarcts, being 30% to 40% more prevalent in women.

A critical issue is the distinction between lacunar infarcts and dilated Virchow-Robin perivascular spaces. The latter are often <3 mm in size and have a linear or round appearance. Diagnostic criteria for silent brain infarcts vary among the studies. A review found that the majority used a threshold size of ≥3 mm with excellent reliability.[51]

The silent vascular lesions may be located throughout the entire central nervous system, though there is a slight prevalence in the right cerebral hemisphere, probably due to more elusive symptoms of these lesions.[47,48]

Silent brain infarcts increase by two to four times the risk of further ischemic strokes in population-based studies[50,52] and increase the risk of mild cognitive impairment and of overt dementia too.[53-55]

At the moment, no data are available to support a preventive treatment, neither with antiplatelets (in the presence of documented large vessels or in small vessels diseases) nor with anticoagulants (in the presence of cardioembolic sources). Trials aimed to evaluate the treatment of silent strokes could reduce the symptomatic strokes or other adverse outcomes.

Treatment strategies and secondary prevention of cryptogenic stroke

In ischemic stroke of unknown aetiology there is no *evidence-based* treatment to prevent recurrences.[12] A 2015 international survey of three hundred clinicians from 48 countries showed that they prescribed antiplatelet therapy in 94% of CS.[56] Assuming that the majority of CS is due to embolism from the heart or great vessels, for which it has not been possible to diagnose the origin, anticoagulation treatment would have a rational. The WARSS study was the only randomized study that compared treatment with aspirin 325 mg/day *vs* warfarin (international normalized ratio 1.4-2.8) in a subgroup of patients with recent CS according to the TOAST criteria.[57,58] The primary outcome of ischemic stroke or death occurred in 15.0% of those assigned to warfarin *vs* 16.5% of those assigned to aspirin over 2 years [hazard ratio (HR) 0.92, 95% confidence interval (CI) 0.6-1.4]. In the subgroup of patients with cryptogenic stroke whose CT showed an embolic topography, the 2-year rate of absolute reduction was 6% in the group treated with warfarin (18% *vs* 12% HR 0.66 CI 0.4-1.2). In patients who underwent a transesophageal echocardiography the risk was almost halved (9% *vs* 18%);[59] in patients with high NT-pro-BNP, a marker of cardioembolic stroke, the reduction was 70% (P=0.02).[60] Data of sub-groups of WARSS seem to be favourable to the hypothesis that anticoagulation therapy may be more effective than aspirin in patients with cryptogenic stroke in which the lacunar etiology has been excluded. However, that needs to be confirmed by further and more extensive investigation.

Patients with ESUS as defined by cryptogenic stroke/ESUS International Working Group could benefit from oral anticoagulation, in particular with direct inhibitors of Xa and II. In patients with non-valvular atrial fibrillation, new oral anticoagulants had a favourable risk-benefit profile, with significant reductions in stroke, intracranial hemorrhage, and mortality, and with similar major bleeding as warfarin.[61]

Currently, three ongoing Phase III studies are testing new oral anticoagulants efficacy and safety in the prevention of recurrent stroke in patients with ESUS.

The first to start was the RE-SPECT ESUS study (multicenter randomized, double-blind, double-dummy), whose primary endpoint is the reduction in recurrences of ischemic stroke with dabigatran (150 mg or 110 mg twice daily, depending on the age and renal function) compared to aspirin 100 mg once daily. Six thousand patients (3000 per treatment arm) with an ESUS stroke occurred in the previous three months will be recruited and followed up for 6-36 months.

The NAVIGATE ESUS study compare rivaroxaban 15 mg once daily *vs* aspirin 100 mg once daily in 7000 patients, with a mean follow up of 24 months. The primary endpoint is the reduction of any of the components of the composite outcome including stroke (ischemic, hemorrhagic, and undefined stroke, TIA with positive neuroimaging), systemic embolism and first occurrence of major bleeding.

The Atticus study (German multicenter, coordinated by Tübingen University) will randomize 500 patients to demonstrate the superiority of apixaban 5 mg twice daily over 100 mg of aspirin once daily in preventing the occurrence of at least one new ischemic lesion identified by MRI at 12 months when compared to the baseline MRI (both DW and fluid attenuation inversion recovery) obtained at the time of study drug initiation.

The results of these three trials are expected to confirm the effectiveness and safety of treatment with new

oral anticoagulants in cryptogenic stroke and if the ESUS construct is only a theoretical exercise or not.

Future directions

The large number of strokes actually classified as CS suggests the inadequacy either of the classification criteria adopted or of the instrumental diagnostic approach in stroke of undetermined origin, in particular in real life. An interesting paper recently published,[56] concerning a 18-question online survey administered to 995 physicians involved in stroke care in 61 countries (mainly high-income and in Europe, Central Asia and North America), shows that only a limited number of CS patients underwent all the exams which are considered relevant and therefore required for the definition of the etiology of a stroke. In particular, transesophageal echocardiography is routinely done in only 17% of hospitals, while 24 h Holter cardiac rhythm monitoring is performed only in 41% of hospitals and extended cardiac rhythm monitoring for more than 24 h is done at 17% of hospitals. That clearly indicates how a more complete and widespread approach to CS is needed in order to reduce the proportion of patients in which stroke is classified of undetermined origin. Another suggestion for the future is represented by the encouragement to a more regular investigation of uncommon causes of stroke like cervical artery dissection, vasculitides, pulmonary fistulae, antiphospholipid syndrome, genetic thrombophilic disease, Fabry's disease, occult cancer.[62] Due to the frequent identification of cardiac arrhythmias during ECG monitoring in the acute phase of stroke, it is also relevant to admit all stroke patients to monitored stroke unit, which according to evidence can ameliorate either short- or long-term prognosis of stroke patients. The development of new instrumental techniques (imaging, blood biomarkers, cardiac function exploration) will simplify the diagnostic approach to stroke and will help to identify rare causes of ischemic brain damage. However, only an adequate diffusion of these diagnostic instruments, together with the application of the complete diagnostic setting in all Stroke Units will significantly reduce the burden of undetermined (and therefore cryptogenic) stroke.

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