

# Classification of Stroke Subtypes

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## Key Words

Stroke · Classification systems · Review

## Abstract

This article reviews published stroke subtype classification systems and offers rules and a basis for a new way to subtype stroke patients. Stroke subtyping can have different purposes, e.g. describing patients' characteristics in a clinical trial, grouping patients in an epidemiological study, careful phenotyping of patients in a genetic study, and classifying patients for therapeutic decision-making in daily practice. The classification should distinguish between ischemic and hemorrhagic stroke, subarachnoid hemorrhage, cerebral venous thrombosis, and spinal cord stroke. Regarding the 4 main categories of etiologies of ischemic stroke (i.e. atherothrombotic, small vessel disease, cardioembolic, and other causes), the classification should reflect the most likely etiology without neglecting the vascular conditions that are also found (e.g. evidence of small vessel disease in the presence of severe large vessel obstructions). Phenotypes of large cohorts can also be characterized by surrogate markers or intermediate phenotypes (e.g. presence of internal carotid artery plaque, intima-media thickness of the common carotid artery, leukoaraiosis, microbleeds, or multiple lacunae). Parallel classifications (i.e. surrogate markers) may serve as within-study abnormalities to support research findings.

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## Introduction

Stroke is a heterogeneous disease with more than 150 known causes. Most registries have failed to identify a definite cause in 25–39% of patients, depending on the quality, completeness, and rapidity of the work-up. This group of strokes of unknown causes (the so-called 'cryptogenic strokes', a term popular among neurologists but perhaps unnecessarily cryptic to students, patients, and most nonstroke physicians) should be a major focus for future clinical research.

Subtyping ischemic stroke can have different purposes, e.g. describing patients' characteristics in a clinical trial, grouping patients in an epidemiological study, careful phenotyping of patients in a genetic study, and classifying patients for therapeutic decision-making in daily practice. Most epidemiological studies have failed to find a link between blood-cholesterol levels and stroke, but studies that looked at some subtyping (ischemic vs. hemorrhagic stroke) did find such a relation. Other large epidemiological studies have found a strong association between carotid stenosis and blood cholesterol levels. Although carotid stenosis is a cause of stroke, serum cholesterol levels have not been associated with atherothrombotic stroke because no epidemiologic studies have properly looked for this association in this particular subtype of ischemic stroke.

In addition to subtyping ischemic stroke, depending on the question being asked in clinical research, it can be useful to further characterize the cohort by intermediate phenotypes (e.g. presence of internal carotid artery plaque, intima-media thickness of the common carotid artery, or presence of leukoaraiosis, microbleeds, or multiple lacunae on magnetic resonance imaging). Since all of these subtyping approaches have their own biases, using different approaches in parallel (i.e. ischemic stroke subtyping and intermediate phenotype) may serve as a within-study method of replication to support research findings.

### Justifications for a New Classification for Ischemic Stroke Subtyping

#### *Stroke Data Bank Subtype Classification*

Derived from the Harvard Stroke Registry classification [1], the National Institute of Neurological Disorders and Stroke (NINDS) Stroke Data Bank recognized 5 major groups: brain hemorrhages; brain infarctions, and among them atherothrombotic and tandem arterial pathological abnormalities; cardioembolic stroke; lacunar stroke; and stroke from rare causes or undetermined etiology (table 1) [2].

#### *Weaknesses of this classification:*

- The very restrictive definition for atherothrombotic stroke (the investigators selected only patients with  $\geq 90\%$  stenosis), resulting in an evident underestimation of the overall burden of atherothrombotic disease (9% of the entire cohort were in the atherothrombotic group).
- The wide definition for lacunar strokes without asking for either assessment of intracranial arteries or additional old lacunar-type infarcts or small-vessel-related parenchymal abnormalities on brain imaging. Modern MRI with diffusion-weighted imaging was not used at the time.
- The evident overestimation of the group of 'undetermined' etiology (39% of the cohort), not only because the newer diagnostic tools were not available at that time (e.g. transesophageal echocardiography, TEE, magnetic resonance angiography, MRA, duplex ultrasound examination, and transcranial Doppler), but also because of the restrictive definition of atherothrombotic causes and the inclusion in this group of patients with tandem lesions.

#### *Strength of this classification:*

- Only patients with atherothrombosis likely to be causally related to stroke could be included in the group classified as having atherothrombotic stroke, with a large group of other individuals classified as having 'stroke of unknown cause'. This approach could be the best option in the search of new causes of stroke among patients with no known cause or with disease not causally related to the stroke event.

#### *Oxfordshire Community Stroke Project Subtype Classification*

The classification from the Oxfordshire Community Stroke Project (OCSP) was proposed to characterize this population-based epidemiological study [3, 4]. The investigators had to cope with the quality and cost of the work-up available at that time in the UK. Transient ischemic attacks (TIA) and strokes were detected and investigated by general practitioners. The classification was based on clinical findings only. Computed tomography (CT) scanning was the best investigational test performed, but assessment of extra- and intracranial arteries and precise cardiac work-up were not available. This likely led the OCSP investigators to classify patients according to the extent and site of brain infarction on clinical grounds alone (table 2).

#### *Weaknesses of this classification:*

- The extent and site of the brain infarct is unlikely to be specific to a particular stroke etiology.
- Patients classified as having a lacunar infarct may have a missed M1 stenosis or a cardiac source of embolism.
- This classification should no longer be used in the 21st century to investigate potential risk factors or causes of stroke.

#### *Strengths of this classification:*

- Patients are easy to classify into groups based on clinical grounds and CT scanning, which is done in almost all patients.
- The outcome of stroke is driven strongly by the severity of the stroke, which is well reflected in this classification, without addressing the cause of the stroke (i.e. without a complete work-up).

#### *Trial of ORG 10172 in Acute Stroke Treatment Subtype Classification*

Since 1993, most clinical researchers used the classification proposed by the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) investigators. The original purpose of this classification was to better characterize

the TOAST cohort of patients in order to investigate the potential efficacy of danaparoid in various stroke subtypes [5]. The TOAST investigators defined 11 categories of stroke, which were further collapsed into 5 groups (table 1). Only these 5 groups were used in further clinical research [6]. Consequently, use of the TOAST classification can mask the paucity of clinical investigations on the one hand, and does not account for a very precise work-up on the other. This is the necessary goal in the database of a multicentre trial such as TOAST, but may not systematically apply to all other types of clinical research.

Despite this, the TOAST classification system has become the most widely used in recent literature, most often in studies that did not investigate the efficacy of new acute stroke treatments, such as genetic association studies, evaluations of new potential risk factors or causes of stroke, epidemiologic studies, etc. Consequently, we question the accuracy and utility of the TOAST classification for research goals other than acute-phase treatment trials.

*Weaknesses of this classification:*

- Small vessel (lacunar) stroke is defined by the clinical syndrome and the size of the infarct. Consequently, a single small deep infarct due to M1 middle cerebral artery atherosclerotic stenosis could be classified by researchers as small vessel disease if an appropriate M1 middle cerebral artery evaluation has not been performed.
- Cardiac sources of embolism are further classified as high or medium risk. Consequently, a patient with V3 vertebral artery dissection ignored by a late negative or incomplete work-up and with a patent foramen ovale (PFO) can be classified by the clinical researcher as a ‘cardiac embolism’.
- Stroke of undetermined cause is the most heterogeneous group in the TOAST classification system, as in the Stroke Data Bank, with patients having at least 2 definite potential causes grouped with those with an entirely negative work-up, and with patients with documented atherosclerotic disease who did not reach the 50% stenosis limit required to qualify for atherothrombotic stroke. Thus, when looking at genetic-association studies or potential risk factors such as serum cholesterol or a potential new cause such as PFO or antiphospholipid antibodies, clinical researchers introduced a major bias.
- This classification system could also flaw the medical decision-making process. For example, the TOAST classification allows many clinicians to oversize the ‘stroke of undetermined etiology’ group (table 1), into which patients with small vessel disease, patients with

a ‘missed’ diagnosis of dissection (by ignorance or by insufficient or late work-up), and patients with several risk factors or documented atherosclerotic disease that does not fit into the ‘atherothrombotic’ group can fall (table 1). Oversizing this group may lead, for example, to inappropriately close thousands of innocent PFO [7].

*Strengths of this classification:*

- The reliability of the classification has been improved by the use of a computerized algorithm, and variability can be addressed by having 2 raters classify each case. [8] This does not, however, overcome the criticisms outlined above.
- Another algorithm has been proposed by adding 3 subcategories to the 11 groups (i.e. evident, probable, or possible), allowing the authors to decrease the size of the group of undetermined cause from 40 to 4% with a  $\kappa$  value of 0.90 versus 0.78 for the original TOAST classification [9]. However, one could question whether having only 4% of patients in the unknown-cause group by ‘forcing’ the classification of other patients into the 11 categories by accepting a weak level of evidence is really of help when the research purpose is to phenotype the cohort for genetic studies or to find new potential causes of stroke among the group of unknown cause.

Many other classifications have been proposed, such as those from the Lausanne Stroke Registry and the Étude du profil Génétique de l’Infarctus Cérébral (GÉNIC) study (table 1) [10, 11]. In the Lausanne Stroke Registry, the group with stroke of unknown cause was one of the least important, widening the atherothrombotic group by the inclusion of patients with stenosis <50% or plaques or with at least 2 risk factors. This actually accounted for the true prevalence of atherothrombotic disease from a preventive treatment point of view, but also likely overestimated the atherothrombotic causative relationship with the brain infarct. The GÉNIC classification also tended to overestimate the atherothrombotic group by including patients with any carotid stenosis >30% in this group. This approach was justified by the need to identify all patients with atherothrombosis for a genetic phenotyping purpose, irrespective of stroke cause, provided that there were no cardiac sources of embolism, no suspicion of lacunar stroke, and no rare causes of stroke.

**Table 1.** Stroke subtype classifications: Stroke Data Bank, Lausanne Stroke Registry, TOAST and GÉNIC

Stroke Data Bank	TOAST classification	Lausanne Stroke Registry	GÉNIC classification
<p><b>Atherothrombosis:</b></p> <ul style="list-style-type: none"> <li>- &gt;90% stenosis or occlusion on angiography of the internal carotid artery origin or siphon, BA, or major cerebral artery stem;</li> <li>- high convexity infarction on CT attributed to hemodynamic insufficiency if it was accompanied by an ipsilateral TIA within the previous 30 days;</li> <li>- ipsilateral bruit or prior TIA.</li> </ul>	<p><b>Large-artery atherosclerosis:</b></p> <ul style="list-style-type: none"> <li>- &gt;50% stenosis or occlusion of a major brain artery or branch cortical artery, presumably due to atherosclerosis (cortical or cerebellar dysfunction; no lacunar syndrome; cortical, cerebellar, brain stem or subcortical infarct &gt;1.5 cm; stenosis of extracranial internal carotid artery; no other abnormalities on tests);</li> <li>- no cardiac source of embolism;</li> <li>- no subcortical or brainstem infarct &lt;1.5 cm.</li> </ul>	<p><b>Atherosclerosis with stenosis:</b></p> <ul style="list-style-type: none"> <li>- &gt;50% stenosis of corresponding extra- or intracranial artery (MCA, PCA, BA) in the absence of another cause.</li> </ul>	<p><b>Atherothrombotic strokes:</b></p> <ul style="list-style-type: none"> <li>- defined by: (1) an ipsilateral internal carotid stenosis &gt;30%, (2) an ipsilateral stenosis &gt;50% of another intra- or extracranial artery, or (3) plaques &gt;4 mm in the aortic arch with a mobile component.</li> </ul>
<p><b>Tandem arterial pathology:</b></p> <ul style="list-style-type: none"> <li>- extracranial lesion insufficient in itself to account for stroke on hemodynamic grounds, but possibly served as an embolic source;</li> <li>- supportive data: hemispherical surface infarct; relevant stenosis of &gt;75%, single ulcer &gt;2 mm in depth or multiple craters in the internal carotid artery, and &gt;50% stenosis of any major cerebral artery stem or the BA.</li> </ul>		<p><b>Atherosclerosis without stenosis:</b></p> <ul style="list-style-type: none"> <li>- plaques or &lt;50% stenosis of corresponding extra- or intracranial artery (MCA, PCA, BA) in the absence of another cause;</li> <li>- and in patients with <math>\geq 2</math> of the following risk factors: age <math>\geq 50</math> years, hypertension, diabetes mellitus, cigarette smoking, or hypercholesterolemia.</li> </ul>	
<p><b>Cardiac embolism:</b></p> <ul style="list-style-type: none"> <li>- cardiac source recognized: AF or flutter, bacterial or marantic endocarditis, mitral annulus calcification, myocardial infarction within prior 6 weeks, atrial myxoma, mitral valve prolapse, right-to-left cardiac shunts, and pulmonary vein thromboses.</li> </ul>	<p><b>Cardioembolism:</b></p> <ul style="list-style-type: none"> <li>- high-risk [mechanical prosthetic valve, mitral stenosis with AF, AF other than lone AF, left atrial/atrial appendage thrombus, sick sinus syndrome, recent myocardial infarction (&lt;4 weeks), left ventricular thrombus, dilated cardiomyopathy, akinetic left ventricular segment, atrial myxoma, infective endocarditis];</li> <li>- medium risk [mitral valve prolapse, mitral annulus calcification, mitral stenosis without AF, left atrial turbulence (smoke), atrial septal aneurysm, patent foramen ovale, atrial flutter, lone AF, bioprosthetic cardiac valve, nonbacterial thrombotic endocarditis, congestive heart failure, hypokinetic left ventricular segment, myocardial infarction &gt;4 weeks and &lt;6 months].</li> </ul>	<p><b>Emboligenic heart disease:</b></p> <ul style="list-style-type: none"> <li>- Intracardiac thrombus or tumor, rheumatic mitral stenosis, prosthetic aortic or mitral valves, endocarditis, AF, sick sinus syndrome, left ventricular aneurysm or akinesia after myocardial infarct, acute (&lt;3 months) myocardial infarct, or global cardiac hypokinesia or dyskinesia in the absence of another cause.</li> </ul>	<p><b>Cardioembolic stroke:</b></p> <ul style="list-style-type: none"> <li>- patients with mitral stenosis, myocardial infarction within the prior 3 weeks, mural thrombus in left cavities, left ventricular aneurysm, AF with or without spontaneous echocontrast or left atrial thrombus, endocarditis, intracardiac mass.</li> </ul>

<p><b>Lacunar stroke:</b></p> <ul style="list-style-type: none"> <li>– defined by a small deep infarct measuring &lt;15 mm on MRI in the territory corresponding to the symptoms, in a patient presenting a clinical syndrome compatible with the diagnosis of lacune [12];</li> <li>– with no finding to suggest an atherothrombotic or cardioembolic stroke.</li> </ul>	<p><b>Hypertensive arteriopathy:</b></p> <ul style="list-style-type: none"> <li>– infarction in the deep perforating artery in a patient with known hypertension in the absence of another cause.</li> </ul>	<p><b>Small vessel occlusion (lacune):</b></p> <ul style="list-style-type: none"> <li>– one of the traditional clinical lacunar syndromes and no evidence of cerebral cortical dysfunction;</li> <li>– a history of diabetes or hypertension supports the diagnosis;</li> <li>– should have also a normal CT/MRI examination or a relevant brain stem or subcortical hemispheric lesion with a diameter of &lt;1.5 cm;</li> <li>– should not fulfill criteria for large-artery atherosclerosis or cardioembolism (see above).</li> </ul>	<p><b>Lacune:</b></p> <ul style="list-style-type: none"> <li>– lacunar syndrome (pure motor, pure sensory, pure sensorimotor, pure hemiparesis, pure hemichorea, ataxic hemiparesis, or dysarthria clumsy hand syndrome);</li> <li>– small, deep infarct found on CT or a normal CT scan 1 week following the stroke;</li> <li>– if angiography was performed it has to be normal.</li> </ul>
<p><b>Arterial dissection:</b></p> <ul style="list-style-type: none"> <li>– patients with typical clinical-angiographic patterns of carotid/vertebral artery dissection</li> </ul> <p><b>Rare causes:</b></p> <ul style="list-style-type: none"> <li>– patients who had rare causes (e.g. polycythemia vera, thrombocythemia, lupus erythematosus).</li> </ul>	<p><b>Other causes:</b></p> <ul style="list-style-type: none"> <li>– arterial dissection, fibromuscular dysplasia, saccular aneurysm, arteriovenous malformation, cerebral venous thrombosis on angiography, angiitis (multiple segmental arterial narrowing on angiography, pleocytosis of cerebrospinal fluid), hematologic conditions (polycythemia, thrombocythemia, etc.), migraine (history of migraine, occurrence of stroke during an attack of migraine), or other.</li> </ul>	<p><b>Stroke of other determined cause:</b></p> <ul style="list-style-type: none"> <li>– nonatherosclerotic vasculopathies, hypercoagulable states, hematologic disorders;</li> <li>– cardiac source of embolism or large-artery atherosclerosis should be excluded.</li> </ul>	<p><b>Unusual causes:</b></p> <ul style="list-style-type: none"> <li>– arteritis, dissection, fibromuscular hyperplasia, sickle cell anemia;</li> <li>– stroke in the setting of migraine or mycotic aneurysm;</li> <li>– other diagnosed but rare or unusual forms of stroke.</li> </ul>
<p><b>Coexisting causes:</b></p> <ul style="list-style-type: none"> <li>– when 2 or more causes coexist in the same individual.</li> </ul>	<p><b>Mixed causes:</b></p> <ul style="list-style-type: none"> <li>– combinations of the above 4 subtypes.</li> </ul>	<p><b>Stroke of undetermined cause:</b></p> <ul style="list-style-type: none"> <li>– two or more causes identified;</li> <li>– negative evaluation;</li> <li>– incomplete evaluation.</li> </ul>	<p><b>Infarction of undetermined cause:</b></p> <ul style="list-style-type: none"> <li>– diagnosis of exclusion;</li> <li>– no bruit or TIA ipsilateral to the hemisphere affected by the stroke;</li> <li>– no obvious cardiac source of embolism (including occlusion without prior TIA and without a cardiac source of embolism)</li> <li>– normal CT or angiogram.</li> </ul>
<p><b>Unknown causes:</b></p> <ul style="list-style-type: none"> <li>– patients who did not meet criteria for the groups as defined above. These patients may have incidental findings (isolated elevation of antiphospholipid antibodies, patent foramen ovale, atrial septal aneurysm, valvular strands, mitral valve prolapse, mitral annulus calcifications, plaques in the aortic arch without mobile component).</li> </ul>	<p><b>Undetermined cause:</b></p> <ul style="list-style-type: none"> <li>– none of the above causes of cerebral infarction could be determined.</li> </ul>	<p>–</p>	<p>–</p>
<p>–</p>	<p>–</p>	<p>–</p>	<p>–</p>
<p>–</p>	<p>–</p>	<p>–</p>	<p>–</p>

**Table 2.** OCSF classification

Type of infarct	Diagnosis
Cerebral infarction	If a CT scan performed within 28 days of symptom onset shows an area of low attenuation, no relevant abnormality, or an area of irregular high attenuation within a larger area of low attenuation (i.e. an area of hemorrhagic infarction) or: If a necropsy examination shows an area of cerebral infarction (pale or hemorrhagic) in a region compatible with the clinical signs and symptoms.
Lacunar infarct (LACI)	One of the 4 classic clinical lacunar syndromes. Patients with faciobrachial or brachiocrural deficits are included, but more restricted deficits are not.
Total anterior circulation infarct (TACI)	Combination of new higher cerebral dysfunction (e.g. dysphasia, dyscalculia, visuospatial disorders), homonymous visual field defect, and ipsilateral motor and/or sensory deficit of at least 2 areas of the face, arm, and leg. If the conscious level is impaired and formal testing of higher cerebral function or the visual fields is not possible, a deficit is assumed.
Partial anterior circulation infarct (PACI)	Only 2 of the 3 components of the TACI syndrome, with higher dysfunction alone, or with a motor/sensory deficit more restricted than those classified as LACI (e.g. confined to 1 limb, or to the face and hand but not the whole arm).
Posterior circulation infarct (POCI)	Any of the following: ipsilateral cranial nerve palsy with contralateral motor and/or sensory deficit, bilateral motor and/or sensory deficit, disorder of conjugate eye movement, cerebellar dysfunction without ipsilateral long-tract deficit (i.e. ataxic hemiparesis), or isolated homonymous visual field defect.

OCSF = Oxfordshire Community Stroke Project.

### Principles of a Stroke Subtype Classification

A stroke subtype classification should be useful both in daily clinical practice and in epidemiological and genetic studies, randomized acute clinical trials, and prevention studies of various types (e.g. including the hemorrhagic aspects).

- (1) The classification should first distinguish between ischemic and hemorrhagic stroke, subarachnoid hemorrhage, cerebral venous thrombosis, and spinal cord stroke (table 3).
- (2) Regarding the 4 main categories of ischemic stroke (i.e. atherothrombotic, cardioembolic, small vessel disease, and other causes), the classification should

identify the most likely etiology(ies) without neglecting mixed phenotypes (e.g. evidence of small vessel disease in the presence of severe symptomatic atherosclerotic stenosis).

- (3) The classification should be based on patient's medical history, physical examination, and diagnostic tests performed in good time.

#### *What Is a Minimal Diagnostic Evaluation?*

- Assessment of the main risk factors: blood pressure (in the sitting position after 10 minutes of rest, electronic measurement) or a personal history of chronic blood-pressure-lowering treatment, lipid profile, tobacco smoking (current or stopped within the previous 6 months), diabetes mellitus, weight, height, waist circumference, physical exercise versus sedentary lifestyle, and family history of vascular disease; personal history of coronary intervention, acute coronary syndrome or myocardial infarction; and personal history of atrial fibrillation.
- Blood tests: hematocrit, platelets, red and white cell counts, and prothrombin time.
- Electrocardiogram
- Assessment of extracranial arteries (either by carotid ultrasound examination or MRA, or CT angiography, or X-ray angiography).
- Assessment of intracranial arteries (either by transcranial Doppler, and/or MRA, and/or CT angiography, and/or X-ray angiography, and/or high-resolution MRI [12, 13]).
- Specific etiologies:
  - Suspicion of endocarditis needs emergent hemocultures and comprehensive echocardiographic examination;
  - Suspicion of aortic dissection needs emergent thoracic CT or TEE;
  - Suspicion of cerebral artery dissection needs expert ultrasound examination, MRA or X-ray angiography, and fat-saturated MRI in the axial sections to show the hematoma in the arterial wall. This imaging should be performed within 15 days of symptom onset. A late work-up can be normal because the dissection has spontaneously resolved with disappearance of the hematoma in the arterial wall.

#### *When and How to Evaluate Cardiac Cavities and Wall*

- Suspicion of intracardiac thrombus;
- Possibility of intracardiac mass;

- Search for endocarditis, either bacterial or nonbacterial;
- Search for akinetic or aneurismal ventricle;
- Prosthetic valve or clinical suspicion of valvular disease;
- Search for endomyocardial fibrosis;
- Diagnostic tools include transthoracic and transesophageal echocardiography, cardiac CT or cardiac MRI.

#### *When and How to Evaluate the Aorta*

- The thoracic aorta should be evaluated when the cause is unknown (patients not falling into groups 1.1 to 1.5 according to table 3 or patients in group 1.6);
- TEE remains the gold standard; CT angiography and high-resolution MRI are still investigational;
- TEE should be performed by a trained echocardiographer who will look specifically for aortic atheroma during the examination.

#### *When Should TEE Be Performed?*

- When there is a need to assess the right and left atrial cavities;
- When searching for an atrial septal aneurysm;
- When there is a need to assess the thoracic aorta;
- At times, in addition to TEE, a cardiac CT or MRI can help search for a cardiac pathology.

#### *When and How Should a Coronary Artery Disease Be Considered?*

- Patients at high risk of coronary artery disease, such as those with a history of chest pain, diabetes, or documented atherosclerosis in the cerebral arteries;
- Exercise Tl-201 or dipyridamole myocardial scintigraphy;
- CT coronary angiography is still under evaluation;
- X-ray coronary angiography is indicated in patients with a positive myocardial scintigraphy or in patients with acute coronary syndrome.

#### *How Precise Should the Search for Atrial Arrhythmia Be?*

- Continuous monitoring during the acute phase of stroke using a monitor – remote telemetry is helpful when available;
- Holter recording in patients with palpitations;
- Assessment of atrial vulnerability should only be investigational.

**Table 3.** Stroke subtypes

1. Ischemic
1.1. Atherothrombotic
1.1.1. Extracranial
1.1.2. Intracranial
1.2. Small vessel disease (sporadic)
1.3. Cardiac emboli
1.4. Other causes
1.4.1. Dissection
1.4.2. Rare or hereditary large- or medium-sized artery disease (e.g. moya-moya disease, fibromuscular dysplasia)
1.4.3. Rare or hereditary small vessel disease
1.4.4. Coagulopathy
1.4.5. Metabolic disease with arteriopathy
1.4.6. Vasculitis
1.4.7. Other rare entities
1.5. Coexisting causes
1.6. Unknown
1.7. Unclassifiable
2. Hemorrhagic
2.1. Hypertension-related small vessel disease (hemorrhagic type)
2.2. Cerebral amyloid angiopathy
2.2.1. Sporadic
2.2.2. Hereditary
2.3. Bleeding diathesis
2.3.1. Drugs that decrease clotting
2.3.2. Other hemostatic or hematologic disorders
2.4. Vascular malformation
2.4.1. Arteriovenous malformation
2.4.2. Dural fistula
2.4.3. Ruptured aneurysm
2.4.4. Cavernoma
2.4.4.1. Sporadic
2.4.4.2. Familial
2.5. Other causes
2.5.1. Tumor related
2.5.2. Toxic (e.g. sympathomimetic drugs, cocaine)
2.5.3. Trauma
2.5.4. Arteritis, angiitis, endocarditis (ruptured mycotic aneurysm), infections
2.5.5. Rare entities (e.g. dissection of intracranial arteries)
2.6. Coexisting cause
2.7. Unknown
2.8. Unclassifiable
3. Subarachnoid hemorrhage
3.1. With aneurysm
3.2. With dissection
3.3. Traumatic
3.4. Neoplastic (melanoma)
3.5. Unknown
4. Cerebral venous thrombosis
5. Spinal cord stroke
5.1. Ischemic
5.2. Hemorrhagic
5.2.1. Associated with arteriovenous malformation
5.2.2. Associated with coagulopathy

### *For Whom Should a Complete Evaluation of Hemostasis Be Performed?*

- For patients with a family history of thrombophilia;
- For young patients with stroke of unknown cause (group 1.6);
- For patients with suspected cancer-related thrombophilia;
- For patients with associated deep vein thrombosis or pulmonary embolism (mainly if repeated and erratic events);
- Also in patients with recurrent brain embolism in the presence of atrial fibrillation and an international normalized ratio in the therapeutic range.

### *When to Look for Other Causes*

- After quick elimination of atherosclerosis, cardiac sources of embolism, and small vessel disease;
- In stroke patients with unusual clinical features such as fever, systemic inflammation, skin changes, other organ(s) involvement (e.g. pleurisy, splenomegaly, kidney involvement, uveitis), meningitis, and epilepsy.

### *How Rapid Should the Work-Up Be?*

- A late work-up can be normal in a patient with dissection. Here, the patient is falsely classified as having a stroke of unknown cause. Finding a PFO in this patient, or an antiphospholipid antibody concentration of 40 GPL units, could then be misleading and prompt inadequate long-term treatment. This problem is illustrated by the following case study: a 32-year-old woman had dense right-sided hemiplegia at 5:00 a.m. A CT scan showed early signs of a large left pan-hemispheric infarction. At 8:30 am, carotid ultrasound showed left internal carotid artery occlusion. At 9:00 am, TEE showed a large clot moving in the aortic arch at the level of the left common carotid artery. A follow-up TEE was performed 48 h later and the aortic arch was normal, with no evidence remaining of the earlier clot [Amarenco, P., and Cohen, A.A., unpublished data].
- This patient illustrates the importance of rapid work-up. This young woman also had a PFO; if the first TEE had been performed 8 or more days later, many clinicians would have falsely concluded that the PFO had caused the stroke and proposed closing it.
- In both young and elderly patients with stroke of no known cause, every effort should be made to perform a complete cardiac assessment as quickly as possible, and no later than 3–8 days after stroke onset.

### **Approach to Intermediate Phenotype Subtyping**

Examples are carotid plaque or intima-media thickness on ultrasound examination and small vessel disease-related parenchymal abnormalities on MRI.

- Patients have an assessment of the internal carotid artery plaque with ultrasound, or a measurement of the common carotid artery intima-media thickness. With such an approach, the entire cohort (either clinical or epidemiological) can be characterized and analyzed with regard to the presence of atherosclerosis, irrespective of stroke subtype.
- Patients have MRI assessment of the brain parenchyma for leukoaraiosis, dilatation of perivascular spaces, multiple lacunae, and microbleeds; altogether these MRI abnormalities have been associated with small vessel disease. Looking at new risk factors for, or associations with, small vessel disease could either focus on ischemic stroke subtyping (i.e. group 3 of the classification – small vessel disease) or on small vessel disease-related parenchymal abnormalities on MRI with 1, 2, 3, or 4 of these abnormalities, or both.

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