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New Approach to Stroke Subtyping: The A-S-C-O (Phenotypic) Classification of Stroke

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Stroke · Subtype · Severity

Abstract
We now propose a new approach to stroke subtyping. The concept is to introduce a complete 'stroke phenotyping' classification (i.e. stroke etiology and the presence of all underlying diseases, divided by grade of severity) as distinguished from past classifications that subtype strokes by characterizing only the most likely cause(s) of stroke. In this phenotype-based classification, every patient is characterized by A-S-C-O: A for atherosclerosis, S for small vessel disease, C for cardiac source, O for other cause. Each of the 4 phenotypes is graded 1, 2, or 3. One for 'definitely a potential cause of the index stroke', 2 for 'causality uncertain', 3 for 'unlikely a direct cause of the index stroke (but disease is present)'. When the disease is completely absent, the grade is 0; when grading is not possible due to insufficient work-up, the grade is 9. For example, a patient with a 70% ipsilateral symptomatic stenosis, leukoaraiosis, atrial fibrillation, and platelet count of 700,000/mm^3 would be classified as A1-S3-C1-O3. The same patient with a 70% ipsilateral stenosis, no brain imaging, normal ECG, and normal cardiac imaging would be identified as A1-S9-C0-O3. By introducing the 'level of diagnostic evidence', this classification recognizes the completeness, the quality, and the timing of the evaluation to grade the underlying diseases. Diagnostic evidence is graded in levels A, B, or C: A for direct demonstration by gold-standard diagnostic tests or criteria, B for indirect evidence or less sensitive or specific tests or criteria, and C for weak evidence in the absence of specific tests or criteria. With this new way of classifying patients, no information is neglected when the diagnosis is made, treatment can be adapted to the observed phenotypes and the most likely etiology (e.g. grade 1 in 1 of the 4 A-S-C-O phenotypes), and analyses in clinical research can be based on 1 of the 4 phenotypes (e.g. for genetic analysis purpose), while clinical trials can focus on 1 or several of these 4 phenotypes (e.g. focus on patients A1-A2-A3).

Introduction

This classification system defines clinically and pathogenically meaningful groups, while losing as little information as possible. It is factual and not interpretative, and

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Table 1. Methods of classification

Grades of pathology		Levels of diagnostic evidence	
1	Definitely a potential cause of the index stroke	A	Direct demonstration by gold standard diagnostic tests or criteria
2	Causality uncertain	B	By indirect evidence or less sensitive or specific tests or criteria
3	Unlikely a direct cause of the index stroke (but disease is present)	C	By weak evidence

In the absence of disease the grade is 0. In case of insufficient work-up and that the patient cannot be graded, the grade is 9.

Further information can be found in table 2.

based on the minimum number of necessary investigations and a timely work-up to make classification possible. To enable both researchers to use this classification and peer-reviewers of scientific journals to evaluate submitted manuscripts, the level of evidence required for a given patient to be classified into a group must be taken into account.

This new classification system recognizes that many patients belong to several categories; some categories may be causally related to the index stroke, whereas others are simply concurrent. By introducing the 'level of diagnostic evidence', this classification recognizes the completeness, the quality, and the timing of the evaluation to grade the underlying diseases.

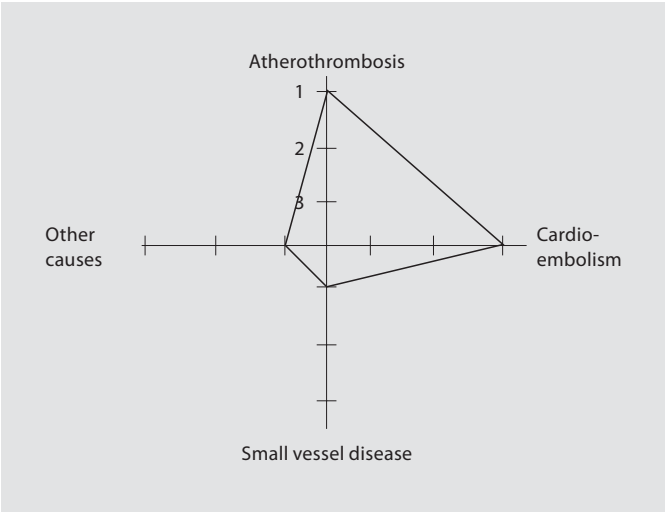

Fig. 1. Example of the grading system (phenotyping) in 1 patient with an ipsilateral carotid stenosis >70% (atherothrombosis, grade 1) and atrial fibrillation (cardioembolism, grade 1), leukoaraiosis and microbleeds (small vessel disease, grade 3), and platelet count of 700,000/mm^3 (other causes, grade 3). Stroke subtype is A1-S3-C1-03.

Methods of A-S-C-O Classification

The methods of this classification are clearly laid out in tables 1–3. Patients are evaluated for 4 predefined phenotypes, i.e. atherosclerosis (A), small vessel disease (S), cardiac disease (C), and other causes (O).

The first step is to 'grade' every patient in each of the 4 main ischemic groups (i.e. atherothrombotic, cardioembolic, small-vessel disease, and other causes) as we do in everyday clinical practice (table 2; fig. 1).

Three grades of likelihood are considered (table 1):

- Grade 1: definitely a potential cause of the index stroke;
- Grade 2: causality uncertain;
- Grade 3: unlikely a direct cause of the index stroke (but disease is present).

In addition, when no disease is present patients are graded 0; patients who cannot be graded because no tests were performed are graded 9.

Three levels are added for the diagnostic instruments used:

- Level A: direct demonstration by gold-standard diagnostic tests or criteria;
- Level B: indirect evidence or less sensitive or specific tests or criteria;
- Level C: weak evidence in the absence of specific tests or criteria.

Every patient is identified by A-S-C-O: for example a patient with a 70% ipsilateral symptomatic stenosis, leukoaraiosis, atrial fibrillation and platelet count of 700,000/mm^3 will be classified A1-S3-C1-O3 (fig. 1). Given the criteria and definitions in table 2, an electronic algorithm can be developed for bedside use (available on www.asco-classification.org).

The next step is optional. According to the specific A-S-C-O pattern, the patient may have only 1 potential cause (corresponding to grade 1 in 1 of the 4 A-S-C-O phenotypes) or may have several potential causes (coexisting cause group), provided this is based on A or B evidence diagnostic test.

Table 2. Grades of pathology (phenotyping)

Grades for atherothrombosis (A)	
1. Definitely a potential cause of the index stroke	Atherothrombotic stroke defined as: (a) Patients with any atherosclerotic stenosis 70–99% in an intra-/or extracranial artery supplying the ischemic field diagnosed by level A or B evidence; or (b) Any atherosclerotic stenosis <70% in an intra-/or extracranial artery supplying the ischemic field with attached luminal thrombus diagnosed by level A or B evidence; or (c) A mobile thrombus in the aortic arch; or (d) Occlusion with imaging evidence of atherosclerosis in an intra-/or extracranial artery supplying the ischemic field.
2. Causality uncertain	(a) Patients with any atherosclerotic stenosis 70–99% in an intra-/or extracranial artery supplying the ischemic field diagnosed by level C evidence; or (b) Any atherosclerotic stenosis <70% in an intra-/or extracranial artery supplying the ischemic field with attached luminal thrombus diagnosed by level C evidence; or (c) Aortic arch plaques >4 mm in thickness without a mobile component.
3. Unlikely a direct cause of index stroke (but disease is present)	(a) Presence of carotid or vertebral artery plaque without stenosis; or (b) Aortic arch plaque <4 mm; or (c) Stenosis (any degree) in a brain artery, contralateral to the brain infarction or in the opposite circulation (either posterior or anterior circulation); or (d) History of myocardial infarction or coronary revascularization or peripheral arterial disease.
Grades for small vessel disease (S)	
1. Definitely a potential cause of the index stroke	Association of: (a) Deep branch artery stroke: small, deep infarct with diameter <15 mm on MRI (or CT) in the territory corresponding to symptoms; and either (b) One or several old or silent lacunar infarcts in territories different from the index stroke; or (c) Leukoaraiosis on MRI (or CT), microbleeds on MRI (gradient echo imaging), dilatation of the perivascular spaces on MRI (or CT); or (d) Recent repeated similar TIAs – when they preceded the brain infarct by 1 month or less and attributable to the same territory as the subsequent BI (which increase the prediction for lacunar stroke from 57 to 80%, and are therefore supportive).
2. Causality uncertain	(a) Single, deep branch artery stroke; or (b) Clinical syndrome suggestive of deep branch artery stroke with no MRI/CT evidence of stroke (clinical syndrome suggestive of a deep branch artery stroke – classic lacunar syndromes: pure motor hemiparesis, pure sensory syndrome, ataxic hemiparesis, dysarthria clumsy-hand syndrome, and sensorimotor syndrome; or other 'nonlacunar' clinical syndromes. e.g. hemichorea, hemiballism, isolated dysarthria, etc.).
3. Unlikely a direct cause of index stroke (but disease is present)	Leukoaraiosis on MRI (or CT), and/or microbleeds on MRI (gradient echo imaging), and/or dilatation of perivascular spaces on MRI (or CT), and/or one or several lacunar infarcts (silent or old) in territories different from the index stroke.
Grades for cardioembolism (C)	
1. Definitely a potential cause of the index stroke	Cardioembolic stroke – demonstration of: (a) Mitral stenosis; (b) Prosthetic heart valve; (c) Myocardial infarction within the past 4 weeks; (d) Mural thrombus in left cavities; (e) Left ventricular aneurysm; (f) Any documented history or permanent or transient atrial fibrillation or flutter with or without spontaneous echo contrast or left atrial thrombus; (g) Sick sinus syndrome;

Table 2 (continued)

Grades for cardioembolism (C)		
	(h)	Dilated cardiomyopathy;
	(i)	Ejection fraction <35%;
	(j)	Endocarditis;
	(k)	Intracardiac mass;
	(l)	PFO plus in situ thrombosis;
	(m)	PFO plus concomitant PE or DVT preceding the brain infarction.
2. Causality uncertain	(a)	PFO and ASA;
	(b)	PFO and concomitant DVT or PE (but not preceding the index stroke);
	(c)	Spontaneous echo contrast;
	(d)	Apical akinesia of the left ventricle and impaired ejection fraction (but >35%);
	(e)	Only suggested by history of myocardial infarction or palpitation and multiple repeated brain infarcts on both sides or in both the anterior and posterior circulation;
	(f)	Only suggested by abdominal CT/MRI or autopsy demonstration of the presence of systemic infarction (e.g. kidney, splenic, mesenteric) or lower limb embolism (in addition to the index stroke).
3. Unlikely a direct cause of index stroke		One of the following abnormalities: PFO, ASA, valvular strands, mitral annulus calcification, calcified aortic valve, nonapical akinesia of the left ventricle.
Grades for other causes (O)		
1. Definitely a potential cause of the index stroke (examples)	(a)	Arterial dissection by A or B evidence (table 3);
	(b)	Dolichoectasia with complicated aneurysm;
	(c)	Polycythemia vera, thrombocythemia >800,000/mm^3;
	(d)	Lupus erythematosus;
	(e)	Disseminated intravascular coagulation;
	(f)	Criteria for antiphospholipid antibody syndrome;
	(g)	Fabry's disease;
	(h)	Concomitant meningitis;
	(i)	Sickle cell disease;
	(j)	Ruptured cerebral aneurysm with or without demonstration of spasm in the territory of the brain infarct;
	(k)	Homozygote for hyperhomocystinuria.
2. Causality uncertain	(a)	Arterial dissection diagnosed by level C evidence (see table 3; only suggestive history or clinical syndrome, e.g. isolated acute painful Horner's syndrome, or only history of previous dissection);
	(b)	Fibromuscular dysplasia.
3. Unlikely a direct cause of index stroke (but disease is present)	(a)	Kinking or dolichoectasia without complicated aneurysm or plicature;
	(b)	Arteriovenous malformation or saccular aneurysm;
	(c)	Thrombocytosis >450,000 and <800,000/mm^3;
	(d)	Antiphospholipid antibodies <100 GPL units;
	(e)	Mild hyperhomocysteinemia heterozygote.

TIA = Transient ischemic attack; BI = brain infarction; PFO = patent foramen ovale; PE = pulmonary embolism; ASA = Atrial septal aneurysm; DVT = deep vein thrombosis. In the absence of disease the grade is 0. In case of insufficient work-up and that the patient cannot be graded, the grade is 9.

Table 3. Levels of diagnostic evidence

Level A: Direct demonstration by gold standard diagnostic tests or criteria	Level B: Indirect evidence or less sensitive or specific tests or criteria	Level C: Weak evidence
Arterial stenosis		
– By autopsy evidence (macro- and microscopic demonstration) of atherosclerotic disease of the arterial wall; – Lumen stenosis by X-ray angiography, or high-resolution MRI, or combination of MR-angiography and Duplex echography for ICAO stenosis with concurring results.	– By only 1 of the following diagnostic tests: duplex, TCD, CT-angiography or MR angiography.	– Carotid bruit only; – Low flow retinopathy; – Reversed flow of fronto-orbital artery on continuous wave Doppler; – Asymmetric blood pressure on both brachial artery (for subclavian or innominate artery stenosis).
Ruling out stenosis: Extracranial arterial stenosis: 1 or several of the following diagnostic tests are performed and are negative: Duplex, CTA, MRA, XRA. Intracranial arterial stenosis: 1 or several of the following diagnostic tests are performed and are negative: TCD, CTA, MRA, XRA. Aortic arch atheroma: TEE with specific assessment of the aortic arch (when the probe is pulled back at the end of the cardiac examination, turn the probe counterclockwise and take time to watch the aortic arch).		
Small vessel disease stroke		
Ruling out small vessel disease stroke: Negative MRI (T_2, FLAIR, GRE, DWI) and no appropriate clinical syndrome suggestive of a deep branch artery stroke.		
Cardiac disease		
– TEE for: valvular disease, atrial and aortic thrombus, atrial tumor or endocarditis; – TTE for: left ventricle mural thrombus or endomyocardial fibrosis; – Cardiac ultra-fast CT or MRI for some cardiac pathologies (intracardiac thrombi, a tumor, endomyocardial fibrosis); – Pathology (autopsy evidence, macro- and microscopic demonstration of a cardiac source of embolism); – ECG documentation for atrial fibrillation; – Combined ECG and biologic (troponin) documentation for myocardial infarction; or pathology (autopsy evidence, macro- and microscopic demonstration of MI).	– Clinical auscultation by a cardiologist for valve disease	–
Ruling out a cardiac source of embolism: Minimum is negative ECG and auscultation by a cardiologist; Maximum is negative ECG/telemetry/Holter ECG and negative TEE, negative cardiac CT/MRI, negative abdominal CT/MRI (search for old or simultaneous subdiaphragmatic visceral infarction). *Ruling out a PFO by best available technology:* Microbubble injections with Valsalva maneuver; With assessment by either TCD of the MCA or TTE (TTE usually allows a better Valsalva maneuver than under TEE). In case of a negative TTE/TEE, if one doubts the quality of the technique used to search for microbubbles crossing, a confirmation can be obtained by TCD technique: negative results in both techniques is the gold standard for ruling out PFO.		

Table 3 (continued)

Level A: Direct demonstration by gold standard diagnostic tests or criteria	Level B: Indirect evidence or less sensitive or specific tests or criteria	Level C: Weak evidence
Arterial dissection		
– Evidence of mural hematoma within the arterial wall by: axial T_1-FatSat-MRI or pathology (autopsy evidence); on some occasions axial CT or TOF-MRA may also show the mural hematoma.	– Presence of lumen stenosis: by X-ray angiography showing typical long stenosis beyond carotid artery bifurcation or on V2, V3 or V4 segment or by duplex echography or CTA/MRA only.	– Only suggestive history or clinical syndrome (e.g. isolated acute painful Horner's syndrome); – Only history of previous dissection.
Ruling out arterial dissection by the best available technology (key when considering PFO or other weak causality): No sign of dissection on axial T_1-FatSat-MRI or X-ray angiography or pathology (autopsy evidence, macro- and microscopic demonstration of arterial dissection) performed within the appropriate time window (usually within 15 days of stroke onset). Caution: very early MRI assessment may be negative and then positive at follow-up MRI.		
Other causes		
Ruling out other causes: negative: cerebrospinal fluid, complete hemostasis, cerebral arterial imaging and cardiac imaging, family history of inherited disease, inflammatory markers (erythrocyte sedimentation rate, C-reactive protein), hematologic tests (platelet, leucocytes, and eosinophilic counts, hematocrit).		

CT = Computed tomography; CTA = computed tomography angiography; ECG = electrocardiogram; FLAIR = fluid-attenuated inversion recovery; GRE = gradient echo; ICAO = internal carotid artery origin; MI = myocardial infarction; MR = magnetic resonance; MRA = magnetic resonance angiography; MRI = magnetic resonance imaging; PFO = patent foramen ovale; TCD = transcranial Doppler; TEE = transesophageal echocardiography; TOF = time of flight; TTE = transthoracic echocardiography; XRA = X-ray angiography.

When none of the A-S-C-O are 1 (A or B evidence), the cause is unknown, but underlying pathologies may exist (e.g. A2 or A3, or S2 or S3, or C2 or C3, or O2 or O3).

In cases where all A-S-C-O are 0, the cause is completely unknown.

When the patient cannot be classified into 1 of the 4 categories because of insufficient work-up, this stroke patient should not be subtyped (unclassifiable group, graded 9); as an example, a patient with carotid stenosis ≥70% on the symptomatic side who was not evaluated for cardiac source of embolism and had no brain imaging would be identified by A1-S9-C9-O0; if the same patient had an atrial fibrillation on ECG but no cardiac imaging performed, he would be identified by A1-S9-C1-O0; if the same patient had normal ECG but no cardiac imaging performed, he would be classified A1-S9-C9-O0. The higher the proportion of subjects with grade 9, the smaller the overall quality of the study.

Discussion

Compared to the classifications reviewed in the companion paper [1], the main advantages of this new stroke subtyping system are that:

- It follows daily clinical practice: every day at the bedside, we 'grade' or estimate the presence of atherosclerotic disease, small vessel disease, cardiac disease, and other causes of stroke (table 2; fig. 1) for a given patient in order to finally decide which cause(s) is (are) the most likely;
- It retains the best available information, recognizing the overlap between the 4 main categories (fig. 1);
- It informs us about the level of diagnostic evidence (table 3);
- It is highly flexible for use in different purposes including meta-analysis. For example, in genetic studies, phenotyping must be very precise; by using this classification, the researcher can clearly state whether they are addressing small vessel disease grade 1–3 or only small vessel disease grade 1. In clinical trials, this classification better defines the selected population for recruitment; for example, like in most recent antiplatelet trials, the patients recruited would be patients with atherothrombotic stroke grades A1A2A3 in the present classification, small vessel disease grades S1S2S3, C2C3, O3, A0-S0-C0-O0 and with exclusion of patients with cardioembolic stroke grade C1 and other causes grade O1 and O2.

In a manner similar to the success of the classification system for headache put forward by the International Headache Society, the approach chosen in this new stroke classification provides a definition for each category and allows both clinicians and researchers to use a common terminology.

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