

The ASCOD Phenotyping of Ischemic Stroke (Updated ASCO Phenotyping)

P. Amarenco^a J. Bogousslavsky^b L.R. Caplan^c G.A. Donnan^d M.E. Wolf^e
M.G. Hennerici^e

^aINSERM U-698 and Paris-Diderot Sorbonne University, Department of Neurology and Stroke Center, Bichat University Hospital, Paris, France; ^bCenter for Brain and Nervous System Diseases, Genolier Swiss Medical Network, Valmont-Genolier, Glion-sur-Montreux, Switzerland; ^cBeth Israel Deaconess Medical Center, Division of Cerebrovascular Stroke, Boston, Mass., USA; ^dFlorey Institute of Neuroscience and Mental Health, University of Melbourne, Melbourne, Vic., Australia; ^eDepartment of Neurology, University of Heidelberg, Universitätsmedizin Mannheim, Mannheim, Germany

Key Words

Stroke etiology and classification · Stroke subtype

Abstract

ASCO phenotyping (A: atherosclerosis; S: small-vessel disease; C: cardiac pathology; O: other causes) assigns a degree of likelihood of causal relationship to every potential disease (1 for potentially causal, 2 for causality is uncertain, 3 for unlikely causal but the disease is present, 0 for absence of disease, and 9 for insufficient workup to rule out the disease) commonly encountered in ischemic stroke describing all underlying diseases in every patient. In this new evolution of ASCO called ASCOD, we have added a 'D' for dissection, recognizing that dissection is a very frequent disease in young stroke patients. We have also simplified the system by leaving out the 'levels of diagnostic evidence', which has been integrated into grades 9 and 0. Moreover, we have also changed the cutoff for significant carotid or intracranial stenosis from 70% to more commonly used 50% luminal stenosis, and added a cardiogenic stroke pattern using neuroimaging. ASCOD captures and weights the overlap between all underlying diseases present in ischemic stroke patients.

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Introduction

In 2009, we proposed a new system to phenotype patients with ischemic stroke, called ASCO (A for atherosclerosis; S for small-vessel disease, C for cardiac pathology, and O for other causes) to better describe the overlap between diseases underlying a cerebral ischemic event in a stroke patient [1]. Previous stroke subtype classification only considered size and location of cerebral infarction (Oxford classification) or the disease deemed to be directly causally related to the ischemic stroke, neglecting other underlying diseases not deemed to be causally related, although present, such as TOAST and CCS classifications [2].

Based on experience with ASCO during the past few years [3–12], we now propose an updated version called ASCOD phenotyping.

Methods of ASCOD Phenotyping

In ASCOD, every patient should be graded into 5 predefined phenotypes: A (atherosclerosis); S (small-vessel disease); C (cardiac pathology); O (other cause), and D (dissection). As done in the former ASCO classification [1], three degrees of causality between the index ischemic stroke and each category are considered (table 1).

Table 1. Method of classification

Grades of diseases	
1	If the disease is present and can potentially be a cause
2	If the disease is present, but the causal link is uncertain
3	If the disease is present, but the causal link is unlikely
0	If the disease is absent
9	If the workup is insufficient to grade the disease

Table 2. Grades of predefined ASCOD phenotypes

A: Causality grades for atherothrombosis	
A1 (potentially causal)	Atherothrombotic stroke defined as: (1) ipsilateral atherosclerotic stenosis between 50 and 99% in an intra- or extracranial artery supplying the ischemic field; <i>or</i> (2) ipsilateral atherosclerotic stenosis <50% in an intra- or extracranial artery with an endoluminal thrombus supplying the ischemic field; <i>or</i> (3) mobile thrombus in the aortic arch; <i>or</i> (4) ipsilateral arterial occlusion in an intra- or extracranial artery with evidence of underlying atherosclerotic plaque supplying the ischemic field
A2 (causal link is uncertain)	(1) ipsilateral atherosclerotic stenosis 30–50% in an intra- or extracranial artery supplying the ischemic field; <i>or</i> (2) aortic plaque ≥ 4 mm without mobile lesion
A3 (causal link is unlikely, but the disease is present)	(1) plaque (stenosis <30%) in an intra- or extracranial artery, ipsilateral to the infarct area; (2) aortic plaque <4 mm without mobile thrombus; (3) stenosis (any degree) or occlusion in a cerebral artery not supplying the infarct area (e.g. contralateral side or opposite circulation); (4) history of myocardial infarction, coronary revascularization or peripheral arterial disease; (5) ipsi- or bilateral atherosclerotic stenosis 50–99% with bihemispheric MR-DWI lesion
A0 (atherosclerosis not detected)	Ruling out atherosclerosis: (1) extracranial arterial stenosis: one or several of the following diagnostic tests are performed and are negative: US-Duplex, CTA, MRA, XRA, or autopsy; (2) intracranial arterial stenosis: one or several of the following diagnostic tests are performed and are negative: US-TCD, MRA, CTA, XRA, or autopsy; (3) 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 counter clockwise and take time to watch the aortic arch) or specific aortic arch assessment with CTA
A9 (incomplete workup)	US-Duplex, US-TCD or CTA, or MRA, or XRA or autopsy not performed. [A minimum workup is extra- and intracranial assessment of cerebral arteries – maximum workup also includes transesophageal assessment of the aortic arch (or a default CTA of the aortic arch)]
S: Causality grades for small-vessel disease	
S1 (potentially causal)	Combination of: (1) lacunar infarction: small deep infarct <15 mm (in perforator branch territory) on MRI-DWI (or a default CT) in an area corresponding to the symptoms and at least one of the three following criteria: (2) one or several small deep older infarct(s) of lacunar type in other territories, <i>and/or</i> (3) severe (confluent – Fazekas III) leukoaraiosis, or microbleeds, or severe dilatation of perivascular spaces ('état criblé'); (4) repeated, recent (<1 month), TIAs attributable to the same territory as the index infarct
S2 (causal link is uncertain)	(1) only one, recent, lacunar infarction and no other abnormality on MRI (or CT) <i>or</i> (2) clinical syndrome suggestive of a deep branch artery stroke, without ischemic lesion in the appropriate area seen on MRI or CT (main clinical syndrome suggesting a deep branch artery – lacunar – stroke: pure hemiparesis, pure hemisensory loss, ataxic hemiparesis, dysarthria-clumsy hand syndrome, unilateral sensorimotor deficit, others: hemichorea, hemiballism, pure dysarthria, etc.)
S3 (causal link is unlikely, but the disease is present)	Severe (confluent – Fazekas III) leukoaraiosis visible on MRI and/or CT scan, and/or microbleeds visible on T2*-weighted MRI, and/or severe dilatation of perivascular spaces (visible on T2-weighted MRI), and/or one or several old, small deep infarcts of lacunar type

Table 2 (continued)

S0 (small-vessel disease not detected)	Ruling out small-vessel disease stroke: negative MRI (T2, FLAIR, GRE, DWI) and no appropriate clinical syndrome suggestive of a deep branch artery stroke
S9 (incomplete workup)	MRI (or CT) not performed
C: Causality grades for cardiac pathology	
C1 (potentially causal)	Cardiogenic stroke defined as acute, or recent and older bihemispheric or supra- and infratentorial territorial or cortical ischemic lesions and signs of systemic embolism with detection of at least one of the following potential causes: (1) mitral stenosis (surface <1.5 cm ²); (2) mechanical valve; (3) myocardial infarction within 4 weeks preceding the cerebral infarction; (4) mural thrombus in the left cavities; (5) aneurysm of the left ventricle; (6) history or presence of documented atrial fibrillation – whether paroxysmal (>60 s), persistent or permanent – or flutter, with or without left atrial thrombus or spontaneous echo; (7) atrial disease (tachycardia-bradycardia syndrome); (8) dilated or hypertrophic cardiomyopathies; (9) left ventricle ejection fraction <35%; (10) endocarditis; (11) intracardiac mass; (12) PFO <i>and</i> thrombus in situ; (13) PFO <i>and</i> concomitant pulmonary embolism or proximal DVT preceding the index cerebral infarction; (14) aforementioned cardiac pathologies (C1) with single or without obvious cerebral ischemic lesion
C2 (causal link is uncertain)	Regardless of stroke pattern: (1) PFO + atrial septal aneurysm; (2) PFO and pulmonary embolism or proximal DTV concomitant but NOT preceding the index cerebral infarction; (3) intracardiac spontaneous echo-contrast; (4) apical akinesia of the left ventricle and decreased ejection fraction (but >35%); (5) history of myocardial infarction or palpitation and multiple brain infarction, repeated either bilateral or in two different arterial territories (e.g. both anterior and posterior circulation); (6) no direct cardiac source identified, but multiple brain infarction, repeated either bilateral or in two different arterial territories (e.g. both anterior and posterior circulation) and/or evidence of systemic emboli: renal or splenic or mesenteric infarction (on CT, MRI or autopsy) or embolism in peripheral artery supplying arm or leg
C3 (causal link is unlikely, but the disease is present)	One of the following abnormalities present in isolation: PFO, ASA, strands, mitral annulus calcification, calcification aortic valve, nonapical akinesia of the left ventricle, transient atrial fibrillation <60 s, atrial hyperexcitability
C0 (cardiac pathology not detected or not suspected)	Ruling out a cardiac source of embolism: minimum is negative ECG and examination by a cardiologist; maximum is negative ECG/telemetry/24-hour Holter ECG/long-term ECG recording (implantable device, transtelephonic ECG, loop recorder) and negative TEE for atrium, valves and septal abnormalities, negative TTE for PFO and assessment of left ventricle, negative cardiac CT/MRI, negative abdominal CT/MRI (search for old or simultaneous subdiaphragmatic visceral infarction)
C9 (incomplete workup)	Minimum is ECG and examination by a trained cardiologist in the absence of cardiac imaging
O: Causality grades for other causes	
O1 (potentially causal)	(1) dolichoectasia with complicated aneurysm; (2) polycythemia vera or thrombocytopenia >800,000/mm ³ ; (3) systemic lupus; (4) disseminated intravascular coagulation; (5) antiphospholipid antibody syndrome (including >100 GPL units or lupus anticoagulant); (6) Fabry's disease; (7) coexisting meningitis; (8) sickle cell disease; (9) ruptured intracranial aneurysm with or without vasospasm of the artery supplying the infarcted area; (10) severe hyperhomocysteinemia; (11) Horton's disease; (12) other cerebral inflammatory or infectious angitis; (13) moyamoya disease, etc....

Table 2 (continued)

O2 (causal link is uncertain)	(1) saccular aneurysm (with a suspicion of embolism from it) (2) coincidental migraine attack with neurological deficit lasting >60 min in patients with history of migraine aura
O3 (causal link is unlikely but the disease is present)	(1) arteriovenous malformation; (2) thrombocytosis <800,000/mm ³ ; (3) antiphospholipid antibody <100 GPL units; (4) homocysteinemia <40 μmol/l; (5) malignoma with associated hypercoagulation (high D-dimer levels), deep vein thrombosis or pulmonary embolism and/or recent chemotherapy
O0 (no other cause detected)	Ruling out other causes: negative: cerebrospinal fluid, complete hemostasis, cerebral arterial imaging, family history of inherited disease, inflammatory markers (erythrocyte sedimentation rate, C-reactive protein), hematologic tests (platelet, leucocytes, and eosinophilic counts, hematocrit), specific tests according to the suspected disease (e.g. genetic test, retinal angiography for Susac syndrome)
O9 (incomplete workup)	Unable to reasonably exclude other causes based on best available diagnostic tests and stroke-specific history
D: Causality grades for dissection	
D1 (potentially causal)	(1) arterial dissection by direct demonstration (evidence of mural hematoma: hypersignal on FAT-saturated MRI or at autopsy or on TOF-MRA or CT on axial sections showing both enlargement of the arterial wall by the hematoma with narrowing of the lumen or on echography showing an hypoechoic arterial wall with narrowing of the lumen and sudden enlargement of the carotid or vertebral (V2) artery diameter; (2) arterial dissection by indirect demonstration or by less sensitive or less specific diagnostic test (only long arterial stenosis beyond the carotid bifurcation or in V2, V3 or V4 without demonstration of arterial wall hematoma: on X-ray angiography, and/or echography and/or CTA and/or MRA) or unequivocal US with recanalization during follow-up
D2 (causal link is uncertain)	(1) arterial dissection by weak evidence (suggestive clinical history, e.g., painful Horner's syndrome or past history of arterial dissection); (2) imaging evidence of fibromuscular dysplasia of a cerebral artery supplying the ischemic field
D3 (causal link is unlikely but the disease is present)	(1) kinking or dolichoectasia without complicated aneurysm or plicature; (2) fibromuscular dysplasia on arteries not supplying the ischemic field
D0 (no dissection detected or suspected)	Ruling out dissection: negative FAT-saturated MRI of suspected artery or good quality, normal X-ray angiography (too early FAT-saturated MRI performed within 3 days of symptom onset can be falsely negative and then should be repeated). If there is no clinical suspicion of dissection, the patient can be classified D0 provided good-quality extra- or intracranial cerebral artery and cardiac evaluations have been performed
D9 (incomplete workup)	In patients aged less than 60 years and with no evidence of A1, A2, S1, C1, or O1 category: no FAT-saturated MRI performed on the extra- or intracranial artery supplying the ischemic field or no X-ray angiography performed (all performed within 15 days of symptom onset)

To determine the degree of causality, a number of diagnostic tests must be performed. These diagnostic tests are detailed for each category in table 2. If the disease is not detected after a minimum workup has been performed, the grade is 0. In case of incomplete workup (e.g. a minimal workup has not been performed) to rule out the disease, the grade is 9 (tables 1, 2).

Results

In this updated version now called ASCOD phenotyping, we have added a 'D' for dissection, recognizing that dissection is a very frequent causal disease in young ischemic stroke patients. We have also simplified the grading system by leaving out the 'levels of diagnostic evidence'.

This has caused some modifications with regard to technical issues including brain imaging findings, in particular concerning grades C and D. 'Levels of evidence' has now been integrated into grade 9 defined as insufficient workup for each category (table 2). Technical limitations (e.g. poor bone windows for US-TCD or inability to perform MRI) are not necessarily in conflict with full workup. For grade 0 (disease is absent), a separate definition states what is needed to rule out the disease (table 2).

We have also modified the cutoff for significant carotid and intracranial stenosis, from 70% in the previous ASCO, to the more commonly accepted 50% luminal stenosis [13] in ASCOD as well as introduced some additional diagnostic and technical requirements.

Discussion

ASCOD describes all 5 main diseases underlying ischemic stroke that are present or not in a given patient.

Compared to other stroke-subtyping classifications that categorize ischemic stroke in rigid groups into known cause of stroke and undetermined or cryptogenic stroke, ignoring other underlying diseases not deemed to be causally related, ASCOD grades all diseases present in a given patient, captures the overlap between the diseases, and weights the potentially causal relationship between every disease detected and the ischemic stroke [3–7].

By considering every specific disease underlying the ischemic stroke, ASCOD allows a comprehensive analysis of cohorts of patients with ischemic stroke, particularly for the purpose of clinical trials, phenotype-genotype analyses, or evaluation of the pertinence of a new diagnostic test or a new biomarker. ASCOD may help analyze clinical trials and perhaps select patients in future randomized trials.

One of the main advantages of the ASCOD phenotyping is the lack of an ‘undetermined’ or ‘cryptogenic’ group or ‘embolic stroke of unknown source’ (that could also be named ‘embolic stroke of undetected potential sources’). These categories in causative classification systems are too ‘cryptic’, too difficult to define (in fact they are only ‘negatively’ defined) and differ from one neurologist or general practitioner to another, which is frustrating for the patients. With the ASCOD system, the only message to the patient is a positive one. In a patient who has no ASCOD 1 category, we can say that we found specific diseases (grades 2 or 3), but that we are unable to establish a direct causal relationship between these diseases and the ischemic stroke. However, we can treat these diseases according to guideline recommendations to reduce the risk of recurrence.

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