CEREBRAL AUTOSOMAL-DOMINANT ARTERIOPATHY WITH SUBCORTICAL INFARCTS AND LEUKOENCEPHALOPATHY

Cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is associated with mutations in the NOTCH 3 protein, which maps to chromosome 19q12. NOTCH signaling is important in development, but in adults, NOTCH 3 expression is limited to vascular smooth muscle cells, where its function is unknown. Pathologically, there are granular deposits in small cerebral arteries producing ischemic stroke because of vessel wall thickening, fibrosis, and occlusion. These deposits are found in small arteries throughout the body, and diagnosis may be confirmed by the presence of the osmiophilic granules in the basement membrane of vascular smooth muscle cells on skin biopsies.

CADASIL differs from other causes of diffuse subcortical ischemia, such as Binswanger’s disease, by the frequent presence of migraine with or without aura, and individuals with CADASIL are not usually hypertensive. Occasionally, diagnostic confusion may occur with patients with multiple sclerosis, especially the primary progressive type, with the appearance of multiple white matter lesions.

CADASIL often presents in early adulthood, and most affected individuals show symptoms by age 60. In addition to migraine with or without aura, there may be depression and mood disturbances, focal neurological deficits, pseudobulbar palsy, and dementia. Approximately 10% of patients have seizures.

Davous, reviewing extent cases in 1998, proposed clinical diagnostic criteria to formalize the clinical data (Table 1).

PERIVENTRICULAR LEUKOMALACIA

Periventricular leukomalacia consists of multiple ischemic lesions in the periventricular white matter, and is considered to be the main factor responsible for spastic cerebral palsy in premature infants. Diagnostic criteria are in Table 2.

STROKE

The recommended standard World Health Organization definition of stroke is “a focal (or at times global) neurological impairment of sudden onset, and lasting more than 24 hours (or leading to death), and of presumed vascular origin.”

This definition has been employed for decades in many different settings, and has proven to be a valuable tool that may be used irrespective of access to technological equipment. Although many countries have already invested in diagnostic tools, such as neuroimaging, enabling subtyping and more detailed descriptions, the clinical definition remains the standard and is suitable for future studies of stroke. The definition excludes transient ischemic attack, which is defined as focal neurological symptoms lasting less than 24 hours. Subdural or epidural hematoma, poisoning, and symptoms caused by trauma are also excluded.

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Occasionally, a focal brain lesion compatible with a previous stroke is randomly found in patients undergoing neuroimaging for reasons other than stroke. Because **stroke** is a clinical diagnosis, not based on purely radiological findings, this is usually referred to as **silent cerebral infarction**. Thus, if there is no history of corresponding symptoms, the diagnosis of stroke is not met.

### Table 1
**Proposed Diagnostic Criteria for Cerebral Autosomal-Dominant Arteriopathy With Subcortical Infarcts and Leukoencephalopathy**

1. Probable cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL):
   a. Young age at onset (≤50 years of age).
   b. At least two of the following:
      i. Clinical stroke-like episodes with permanent neurological signs.
      ii. Migraine.
      iii. Major mood disturbances.
      iv. “Subcortical-type” dementia.
   c. No vascular risk factor etiologically related to the deficit.
   d. Evidence of an inherited autosomal-dominant transmission.
   e. Abnormal magnetic resonance imaging (MRI) imaging of the white matter without cortical infarcts.

2. Definite CADASIL:
   a. Criteria of probable CADASIL associated with linkage to NOTCH 3 mutation, and/or
   b. Pathological findings demonstrating small vessel arteriopathy with granular osmiophilic material.

3. Possible CADASIL:
   a. Late age at onset (≤50).
   b. Stroke-like episodes without permanent signs, minor mood disturbances, global dementia.
   c. Minor vascular risk factors, such as mild hypertension, mild hyperlipidemia, smoking, and/or use of oral contraceptives.
   d. Unknown or incomplete family pedigree.
   e. Atypical MRI imaging of the white matter.

4. Exclusion criteria:
   a. Age at onset over 70 years.
   b. Severe hypertension or complicated heart or systemic vascular disease.
   c. Absence of any other case in a documented pedigree.
   d. Normal MRI imaging, age over 35 years.


### Table 2
**Criteria for the Neuroimaging Diagnosis of Periventricular Leukomalacia**

I. Serial ultrasonography:
   A. Cyst formation in periventricular area.
   B. Periventricular ultrasonographic echodensity greater than choroid plexus echogenicity.
   C. Findings of B prolonged over 3 weeks with irregularity of lateral ventricular walls and/or less uniform echodensity.

Findings of B or C indicate periventricular leukomalacia, whereas a finding of C indicates possible periventricular leukomalacia.

II. Computed tomography examination:
   A. At 40 weeks, corrected postlast menstrual period, a low density of the periventricular area, and/or centrum semiovale with dilatation and irregularity of lateral ventricle wall suggests periventricular leukomalacia.

III. Magnetic resonance imaging:
   B. After age 11 months, periventricular hypodensities (with dilatation and/or irregularity of lateral ventricular walls) on spin echo T2-weighted image and proton density image are consistent with the diagnosis of periventricular leukomalacia.


Occasionally, a focal brain lesion compatible with a previous stroke is randomly found in patients undergoing neuroimaging for reasons other than stroke. Because **stroke** is a clinical diagnosis, not based on purely radiological findings, this is usually referred to as **silent cerebral infarction**. Thus, if there is no history of corresponding symptoms, the diagnosis of stroke is not met.
Types of Stroke

There are three major stroke subgroups: ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage. Each of the types can produce clinical symptoms that fulfill the definition of stroke; however, they differ with respect to survival and long-term disability.

Ischemic stroke is caused by a sudden occlusion of arteries supplying the brain. The occlusion may either be because of a thrombus formed directly at the site of occlusion (thrombotic ischemic stroke) or be a thrombus formed in another part of the circulation that follows the blood stream until it obstructs arteries in the brain (embolic ischemic stroke). The diagnosis of ischemic stroke is usually based on neuroimaging recordings, but it may not be possible to decide clinically or radiologically whether it is a thrombotic or embolic ischemic stroke.

Intracerebral hemorrhage is a bleeding from one of the brain's arteries into the brain tissue. The lesion causes symptoms that mimic those seen for ischemic stroke. A diagnosis of intracerebral hemorrhage depends on access to neuroimaging, where it can be differentiated from ischemic stroke. Spontaneous intracerebral hemorrhage may be more prevalent in developing countries than in developed countries. The reasons for such differences remain unclear, but variations in diet, physical activity, treatment of hypertension, and genetic predisposition may be responsible.

Subarachnoid hemorrhage is characterized by arterial bleeding in the space between the pia mater and arachnoid layers of the meninges. Typical symptoms are sudden onset of severe headache and usually, impaired consciousness. Symptoms that mimic stroke may occur, but are rare. The diagnosis can be established either by neuroimaging or lumbar puncture.
### Table 4
**Classification of Acute Ischemic Cerebrovascular Syndrome**

<table>
<thead>
<tr>
<th>Category</th>
<th>Definition</th>
<th>Examples</th>
</tr>
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</table>
| Definite acute ischemic cerebrovascular syndrome (AICS) | Acute onset of neurological dysfunction of any severity consistent with focal brain ischemia and imaging/laboratory confirmation of an acute vascular ischemic pathology\(^a\) | 1. Sudden onset of right hemiparesis and aphasia persisting for 3 hours with diffusion-weighted brain imaging (DWI) showing acute ischemic changes.  
2. Twenty-minute episode of left hemisensory loss, which resolved, with acute right thalamic ischemic lesion confirmed on DWI. |
| Probable AICS                                 | Acute onset of neurological dysfunction of any severity suggestive of focal brain ischemic syndrome but without imaging/laboratory confirmation of acute ischemic pathology\(^a\) (diagnostic studies were negative but insensitive for ischemic pathology of the given duration, severity, and location). Imaging, laboratory, and clinical data studies do not suggest nonischemic etiology; possible alternative etiologies are ruled out. | 1. Sudden onset of pure motor hemiplegia that persists with normal computed tomography (CT) at 12 hours after onset. Magnetic resonance imaging (MRI) was not performed.  
2. Ten-minute episode of aphasia and right hemiparesis in a patient with atrial fibrillation and subtherapeutic international normalized ratio. MRI, including DWI, was negative. |
| Possible AICS                                 | Acute neurological dysfunction of any duration or severity possibly consistent with focal brain ischemia without imaging/laboratory confirmation of acute ischemic pathology\(^a\) (diagnostic studies were not performed or were negative and sensitive for ischemic pathology of the given duration, severity and location). Possible alternative etiologies are not ruled out. Symptoms may be nonfocal or difficult to localize. | 1. Two-hour episode of isolated vertigo and headache in a 50-year-old man with a history of hypertension; symptoms resolved at time of imaging. MRI, including DWI, was negative.  
2. Twenty-minute episode of isolated word-finding difficulty in 85-year-old woman with a history of dementia and coronary artery disease. Head CT was negative, and MRI was not performed. |
| Not AICS                                      | Acute onset of neurological dysfunction with imaging/laboratory confirmation of nonischemic pathology\(^a\) (including normal). Imaging/laboratory studies that are highly sensitive for ischemic pathology of the given duration, severity, and location) as the cause of the neurological syndrome. | 1. Sudden onset of left hemiparesis and hemineglect. MRI showed right frontoparietal intracerebral hemorrhage. Imaging/laboratory studies that are highly sensitive for ischemic pathology of the given duration, severity, and location as the cause of the neurological syndrome.  
2. Thirty-year-old man with known seizure disorder found with altered mental status and right hemiplegia. Normal diffusion, perfusion-weighted MRI, and magnetic resonance angiography were acquired while symptoms were still present. Electroencephalogram showed left temporal spikes. |

\(^a\)Imaging/laboratory confirmation includes neuroimaging studies demonstrating recent, appropriately located ischemic lesion (DWI, CT), vascular imaging demonstrating an acute arterial occlusion or stenosis appropriate to the clinical syndrome (transcranial Doppler, magnetic resonance angiography, CT angiography, conventional angiography), or perfusion technique demonstrating a perfusion deficit in an appropriately located vascular distribution (perfusion-weighted MRI, perfusion CT, single photon-emission CT, positron-emission tomography, xenon CT). In the future, additional neuroimaging techniques, such as magnetic resonance spectroscopy or serum/plasma biomarkers specific to acute ischemia, may be identified and could potentially provide similar laboratory confirmation.

(Adapted with permission from Kidwell CS, Warach S. Acute ischemic cerebrovascular syndrome: diagnostic criteria. Stroke 2003; 34:2995–2998.)
Further Definition of Stroke Subtypes

Classification of the stroke events into ischemic or hemorrhagic subtypes relies on access to laboratories and imaging technology. The benefit of using neuroimaging is that some misclassification will occur if clinical assessment alone is used. For example, cancer in the brain may mimic a stroke. Whether an event is hemorrhagic vs ischemic is also of importance from a clinical perspective, as aspirin or other antiplatelet or anticoagulant medication should not be given to patients with hemorrhagic stroke. Studies that include computed tomography (CT) scans in their surveillance system should register days between onset and investigation of the stroke. Preferably, the scan should be conducted within the first 2 weeks, as minor bleedings otherwise may have been absorbed, leading to incorrect classification of the event as ischemic stroke.

An alternative classification of “acute ischemic cerebrovascular syndrome” has been published. It attempts to incorporate imaging findings and laboratory results with clinical findings. This schemata is presented in Table 4.

VASCULAR DEMENTIA

The core of vascular dementia is the presence of dementia and its relationship to cerebrovascular disease (see Table 5). Evaluation of the former is straightforward, but what constitutes vascular disease and what its relationship is to clinical syndromes can be more perplexing. For example, many patients have magnetic resonance imaging findings of periventricular white matter signal change (leuкоaraiosis, such as seen inBinswanger’s disease). In the presence of a progressive dementia typical of Alzheimer’s disease, the clinical picture may be interpreted as vascular dementia owing to small vessel ischemia, or Alzheimer’s disease with “nonspecific” white matter findings. Another example of an unclear case would be an individual, again with findings of progressive dementia, but a single lacunar infarct on neuroimaging. Some clinicians would consider the location of the infarct, with regard to whether it is in an area important for memory dysfunction, whereas others may diagnose a mixed dementing disorder. Because vascular dementia may be the result of a single lesion, the term multi-infarct dementia is not synonymous with vascular dementia.

Overall vascular dementia accounts for 10–20% of all dementia, depending on the population studied. The most common criteria used for diagnosis is the National Institute of Neurological Disorders and Stroke-Associated Internationale pour la Reserche et l’Enseignement en Neurosciences (NINDS-AIREN) criteria (see Table 6). Other criteria included here are the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV), and the Hachinski Ischemia Scale (see Table 7).

The NINDS-AIREN criteria stress the importance of the temporal relation between the vascular event and the onset of dementia. One of the major difficulties with implementing these vascular dementia guidelines is relatively poor interrater agreement in interpretation of neuroimaging studies. Holmes et al. found the sensitivity of the NINDS-AIREN criteria to be only 43%, whereas it had high specificity of 95%.

The DSM-IV guidelines are simpler to follow, but are vague in their requirements for temporal relationships and neuroimaging requirement. It is also unclear whether the presence of a focal deficit, such as aphasia, would be able to be counted in both criterions 1 and 3 because it represents a focal deficit.

The Hachinski criteria were developed using clinical criteria to separate vascular disease from primary degenerative dementia. It was developed at the time when CT scanning was being introduced, and thus has no imaging component. Some studies, particularly those emanating from the Alzheimer’s disease literature, have used different cutoffs in excluding patients. The weighting system has been studied, and Molsa et al. reported that differentiation between populations could be enhanced by assigning varying weights to the variables with the highest discriminatory ability. However, the Hachinski Ischemia Score, as modified by Rosen, remains quite good in distinguishing patients with at least some vascular pathology, as determined in autopsy-based studies.
Table 5
DSM-IV Criteria for the Diagnosis of Vascular Dementia

1. The development of multiple cognitive deficits manifested by both memory impairment (impaired ability to learn new information or to recall previously learned information) and one or more of the following cognitive disturbances:
   a. Aphasia (language disturbance).
   b. Apraxia (impaired ability to carry out motor activities despite intact motor function).
   c. Agnosia (failure to recognize or identify objects despite intact sensory function).
   d. Disturbance in executive functioning (i.e., planning, organizing, sequencing, abstracting).
2. The cognitive deficits in criteria 1a and 1b each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.
3. Focal neurological signs and symptoms (e.g., exaggeration of deep tendon reflexes, extensor plantar response, pseudobulbar palsy, gait abnormalities, weakness of an extremity), or laboratory evidence indicative of cerebrovascular disease (e.g., multiple infarctions involving cortex and underlying white matter) that are judged to be etiologically related to the disturbance.
4. The deficits do not occur exclusively during the course of a delirium.


Table 6
NINDS-AIREN Criteria for the Diagnosis of Vascular Dementia

I. The criteria for the clinical diagnosis of probable vascular dementia include all of the following:
   A. Dementia, defined by cognitive decline from a previously higher level of functioning and manifested by impairment of memory and of two or more cognitive domains (orientation, attention, language, visuospatial functions, executive functions, motor control, and praxis), preferably established by clinical examination and documented by neuropsychological testing; deficits should be severe enough to interfere with activities of daily living not because of physical effects of stroke alone.
   Exclusion criteria: cases with disturbance of consciousness, delirium, psychosis, severe aphasia, or major sensorimotor impairment precluding neuropsychological testing. Also excluded are systemic disorders or other brain diseases (such as Alzheimer’s disease [AD]) that in and of themselves could account for deficits in memory and cognition.
   B. Cerebrovascular disease, defined by the presence of focal signs on neurological examination, such as hemiparesis, lower facial weakness, Babinski sign, sensory deficit, hemianopia, and dysarthria consistent with stroke (with or without history of stroke), and evidence of relevant cerebrovascular disease (CVD) by brain imaging (computed tomography or magnetic resonance imaging [MRI]) including multiple large-vessel infarcts or a single strategically placed infarct (angular gyrus, thalamus, basal forebrain, or posterior cerebral artery or anterior cerebral artery territories), as well as multiple basal ganglia and white matter lacunes, or extensive periventricular white matter lesions, or combinations thereof.
   C. A relationship between the above two disorders, manifested or inferred by the presence of one or more of the following:
      a. Onset of dementia within 3 months following a recognized stroke.
      b. Abrupt deterioration in cognitive functions.
      c. Fluctuating, stepwise progression of cognitive deficits.
II. Clinical features consistent with the diagnosis of probable vascular dementia include the following:
   A. Early presence of gait disturbance (small-step gait or marche a petits pas, or magnetic, apraxic-ataxic or parkinsonian gait).
   B. History of unsteadiness and frequent, unprovoked falls.
   C. Early urinary frequency, urgency, and other urinary symptoms not explained by urological disease.
   D. Pseudobulbar palsy.
   E. Personality and mood changes, abulia, depression, emotional incontinence, or other subcortical deficits including psychomotor retardation and abnormal executive function.

(Continued)
Table 7

Hachinski Ischemia Score

<table>
<thead>
<tr>
<th>Feature</th>
<th>Score</th>
</tr>
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<tbody>
<tr>
<td>Abrupt onset</td>
<td>2</td>
</tr>
<tr>
<td>Stepwise deterioration</td>
<td>1</td>
</tr>
<tr>
<td>Luctuating course</td>
<td>2</td>
</tr>
<tr>
<td>Nocturnal confusion</td>
<td>1</td>
</tr>
<tr>
<td>Relative preservation of personality</td>
<td>1</td>
</tr>
<tr>
<td>Depression</td>
<td>1</td>
</tr>
<tr>
<td>Somatic complaints</td>
<td>1</td>
</tr>
<tr>
<td>Emotional incontinence</td>
<td>1</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>1</td>
</tr>
<tr>
<td>History of strokes</td>
<td>2</td>
</tr>
<tr>
<td>Evidence of associated atherosclerosis</td>
<td>1</td>
</tr>
<tr>
<td>Focal neurological symptoms</td>
<td>2</td>
</tr>
<tr>
<td>Focal neurological signs</td>
<td>2</td>
</tr>
<tr>
<td>Total score:</td>
<td></td>
</tr>
</tbody>
</table>


Imaging in Stroke

Diagnostic criteria from the American Heart Association developed as part of comprehensive standards for the evaluation of transient ischemic attacks and stroke (Tables 8–10).

Table 8

Diagnostic Criteria for Acute Cerebral Infarction, Using Computed Tomography Imaging of the Brain

• Infarction: a focal hypodense area, in cortical, subcortical, or deep gray or white matter, following a vascular territory, or in a “watershed” (also known as “borderzone”) distribution. Early subtle findings may
Table 8 (Continued)

- Include blurring of gray/white matter differentiation, effacement of sulci because of early edema or findings such as “insular ribbon.”
- Hemorrhage: hyperdense image in white or deep gray matter, with or without involvement of cortical surface (40 to 90 Hounsfield units [HU]). “Petechial” refers to scattered hyperdense points, coalescing to form irregularly hyperdense areas with hypodense interruptions. “Hematoma” refers to a solid, homogeneously hyperdense image.
- Hyperdense image in major intracranial artery: suggestive of vascular embolic material (such as the dense middle cerebral artery sign).
- Calcification: hyperdense image within or attached to vessel wall (>120 HU).
- Incidental: silent infarct, subdural collection, tumor, giant aneurysm, arteriovenous malformation.


Table 9

Infarction of the Brain in Magnetic Resonance Imaging in Acute Stroke

- Acute: Subtle, low signal (hypointense) on T1-weighted images, often difficult to see at this stage, and high signal (hyperintense) on spin density and/or T2-weighted and proton density-weighted images starting 8 hours after onset; should follow vascular distribution. Mass effect maximal at 24 hours, sometimes starting 2 hours after onset, even in the absence of parenchymal signal changes. No parenchymal enhancement with a paramagnetic contrast agent, such as gadolinium. Territorial intravascular paramagnetic contrast enhancement of “slow-flow” arteries in hyperacute infarcts; at 48 hours, parenchymal and meningeal enhancement can be expected.
- Subacute (1 week or older): Low signal on T1-weighted images, high signal on T2-weighted images. Follows vascular distribution. Revascularization and blood–brain barrier breakdown may cause parenchymal enhancement with contrast agents.
- Old (several weeks to years): Low signal on T1-weighted images, high signal on T2-weighted images. Mass effect generally disappears after 1 month. Loss of tissue with large infarcts. Parenchymal enhancement fades after several months.


Table 10

Hemorrhage in Magnetic Resonance Imaging of the Brain

<table>
<thead>
<tr>
<th>Age</th>
<th>T1-weighted</th>
<th>T2-weighted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperacute</td>
<td>Hours old, mainly oxyhemoglobin with surrounding edema</td>
<td>Hypointense</td>
</tr>
<tr>
<td>Acute</td>
<td>Days old, mainly deoxyhemoglobin with surrounding edema</td>
<td>Hypointense</td>
</tr>
<tr>
<td>Subacute</td>
<td>Weeks old, mainly methemoglobin</td>
<td>Hyperintense</td>
</tr>
<tr>
<td>Chronic</td>
<td>Years old, hemosiderin slit or hemosiderin margin surrounding fluid cavity</td>
<td>Hypointense</td>
</tr>
</tbody>
</table>

Cerebral Autosomal-Dominant Arteriopathy With Subcortical Infarcts and Leukoencephalopathy


Stroke


Periventricular Leukomalacia


Vascular Dementia


