A COMPREHENSIVE OVERVIEW OF VASCULAR DEMENTIA

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1. INTRODUCTION

• Vascular dementia (VaD) is the second most common cause of dementia, with a frequency ranging from **15% to 25%** at autopsy [1] and a prevalence around **1.5%** in the community in those over 65 years [2-4].

• It represents the most severe vascular cognitive impairment [5].

• Importantly, the diagnosis of vascular cognitive impairment without dementia carries a poor prognosis as it exposes to increased risk of death and dependence [2,6].
1. INTRODUCTION

• Post-stroke dementia should be distinguished from VaD as the former does not always result from pure vascular lesions. Post-stroke dementia corresponds to all dementia observed after a stroke whatever its mechanism.

• Prevalence of poststroke dementia in the community is around 30% [7] and in hospitalized cohort, from 25 to 30% of stroke survivors [8-12].

• About half of these patients meets the criteria of VaD [13,14]; about a third corresponds to mixed dementia (i.e. associated to Alzheimer disease) and the remainder corresponds to other mechanisms [15-17].

• Vascular dementia may be a preventable type of dementia since it results from vascular pathology and usually concerns patients with modifiable vascular risk factors [18]. The diagnosis of VaD has several implications, including a high risk of stroke recurrence and mortality [19].
1. INTRODUCTION

• Vascular dementia results from several vascular pathologies, the most frequent ones being small vessel disease, which is responsible for lacunes and leukoaraiosis (reported in about 40% of post-stroke dementia), and multiple territorial infarcts.

• Because of the vascular mechanisms of underlying lesions, VaD is typically characterized by the frequency of stroke history, abrupt onset, stepwise deterioration, and the early presence of non-cognitive signs such as motor and perceptual deficits, speech and swallowing disorders, gait disorders, frequent falls, and urinary incontinence. The last three signs were found to be the most predictive of VaD [20].
1. INTRODUCTION
Vascular dementia remains probably largely underdiagnosed, as suggested by survey of statistics from stroke unit and memory clinics.

Failure to identify VaD may stem from several difficulties:

1. the under-recognition of dementia in stroke patients is frequently the result of failure to identify cognitive deficits or erroneous attribution of social decline to motor-perceptual deficits [23].

2. the under-recognition of vascular lesions in demented patients may occur because of a lack of stroke history and a stepwise worsening, under-recognition of early non-cognitive neurological signs, or inadequate brain imaging study.

These considerations underline the importance of careful history taken, neurological examination, adequate brain imaging, and neuropsychological studies.
2. DEFINITION AND DIAGNOSTIC CRITERIA FOR VASCULAR DEMENTIA

• The term “vascular dementia” does not correspond actually to a single or specific pathophysiological entity. It characterizes a severe cognitive impairment associated with different types of cerebrovascular disease. For this reason, the course and prognosis of VaD can widely vary according to the underlying vascular disorder.

• Different criteria have been proposed for the definition of VaD. The Diagnostic and Statistical Manual for Mental Disorders, 4th edition (DSM-IV) criteria are sensitive but poorly specific [24].

• When dementia is present, focal neurological signs and symptoms with laboratory evidence indicative of cerebrovascular disease are required to satisfy this definition (Table 1).
### 2. DEFINITION AND DIAGNOSTIC CRITERIA FOR VASCULAR DEMENTIA

**Table 1:**

**Diagnostic and Statistical Manual for Mental Disorders, 4th edition criteria for vascular dementia (DSM-IV)**

<table>
<thead>
<tr>
<th>A1</th>
<th>Memory impairment</th>
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| A2 | One or more of the following cognitive disturbances:  
(a) aphasia  
(b) apraxia  
(c) agnosia  
(d) disturbance in executive functioning |
| B  | Cognitive deficits in criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning |
| C  | Factors judged to be etiologically related to the disturbance:  
(a) focal neurological signs and symptoms  
(b) laboratory evidence indicative of cerebrovascular disease (e.g. multiple infarctions involving cortex and underlying white matter) |
| D  | Not occurring exclusively during the course of delirium |

*Source: American Psychiatric Association [24].*
2. DEFINITION AND DIAGNOSTIC CRITERIA FOR VASCULAR DEMENTIA

• Based on the DSM-IV criteria, patients with Alzheimer disease who had a recent stroke are considered to have VaD. Elsewhere, demented patients without any visible tissue lesions on CT scan and who had transient ischemic attacks and a carotid stenosis will also fulfill the DSM-IV diagnostic criteria for VaD.

• Noteworthily, this broad definition will cover not only “pure” VaD but also mixed dementias (e.g. VaD associated with Alzheimer disease).

• In contrast, the definition proposed by the National Institute of Neurological Disorders and Stroke (NINDS) and the Association Internationale pour la Recherche et l’Enseignement en Neurosciences (AIREN) criteria [25] appear more specific for VaD and are now currently used for research and clinical trials.

• The NINDS-AIREN criteria (Table 2) require the presence of dementia, cerebral tissue lesions known to alter cognitive performances, a temporal relationship between the vascular event and the cognitive alteration, clinical features usually associated with diffuse vascular lesions, and the lack of cognitive decline suggestive of a degenerative process.
2. DEFINITION AND DIAGNOSTIC CRITERIA FOR VASCULAR DEMENTIA

- Although these stenosis will also fulfill the DSM-IV diagnostic criteria for VaD more exactly, this definition will exclude mixed dementia, a frequent cause of cognitive impairment in the elderly and also progressive cognitive decline related to the accumulation of “silent” ischemic or hemorrhagic lesions in the brain. This might contribute to the overall low sensitivity of NINDS-AIREN criteria.

- Other criteria for VaD are available; the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) criteria [26] (Table 3) are close to the DSM-IV criteria but require the evidence of focal brain damage [27].

- The Hachinski Ischemic Score (Table 4) was initially developed to separate multi-infarct dementia related to the accumulation of ischemic lesions (score >7) from Alzheimer disease (score <4) [28].

- The validity of cut-off scores has been supported by recent clinicopathological studies [19]. In a study comparing criteria, Gold et al. [29] showed that Hachinski Ischemic Score was less sensitive (0.43) but more specific (0.88) to VaD compared with NINDS-AIREN criteria (sensitivity: 0.58; specificity: 0.8).
2. DEFINITION AND DIAGNOSTIC CRITERIA FOR VASCULAR DEMENTIA

Table 2. NINDS-AIREN criteria for the diagnosis of probable VaD

1. Dementia
   Impairment of memory
   Impairment of memory and ≥2 cognitive domains
   Orientation
   Attention
   Language
   Visuospatial functions
   Executive functions, motor control and praxis

2. Cerebrovascular disease
   Focal signs on neurological examination (hemiparesis, lower facial weakness, Babinski’s sign, sensory deficit, hemianopia and dyssynergia)
   Evidence of relevant cerebrovascular disease by brain imaging (CT)
   - Large-artery infarcts
   - Single strategically placed infarct
   - Multiple: basal ganglia and white-matter lacunes
   - Extensive periventricular white-matter lesions
   - Combinations thereof

A relationship between the above disorders manifested or inferred by the presence of ≥1 of the following
   - Onset of dementia within 3 months after a recognized stroke
   - Abrupt deterioration in cognitive functions
   - Fluctuating, stepwise progression of cognitive deficits

4. Clinical features consistent with the diagnosis of probable VaD
   - Early presence of a gait disturbance
   - History of unsteadiness or frequent, unprovoked falls
   - Early urinary incontinence
   - Pseudobulbar palsy
   - Personality and mood changes

5. Features that make the diagnosis of VaD uncertain
   - Early onset of memory deficit and progressive worsening of memory and other cognitive functions in the absence of focal neurological signs and cerebrovascular lesions on CT or MRI

Table 3: The International Statistical Classification of Diseases, version 10 research criteria for vascular dementia

A. Evidence of each of the following
   (a) decline in memory (mainly short-term memory)
   (b) decline in other cognitive abilities
   Deficits in criterion A cause a significant impairment of social functioning

B. Absence of clouding of consciousness

C. Decline in emotional control or motivation or a change in social behavior

D. Symptoms in criterion A have been present for ≥6 months
   Unequal distribution of deficits in higher cognitive functions
   Evidence of focal brain damage
   Evidence of cerebrovascular disease

Source: World Health Organization [26].

Table 4: Hachinski Ischemic Score

<table>
<thead>
<tr>
<th>Feature</th>
<th>Score</th>
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<tr>
<td>Abrupt onset</td>
<td>2</td>
</tr>
<tr>
<td>Stepwise deterioration</td>
<td>1</td>
</tr>
<tr>
<td>Fluctuating course</td>
<td>2</td>
</tr>
<tr>
<td>Nocturnal confusion</td>
<td>1</td>
</tr>
<tr>
<td>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 stroke</td>
<td>2</td>
</tr>
<tr>
<td>Associated atherosclerosis</td>
<td>1</td>
</tr>
<tr>
<td>Focal neurological symptoms</td>
<td>2</td>
</tr>
<tr>
<td>Focal neurological signs</td>
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A score of 4 or less suggests dementia is due to Alzheimer’s disease, a score of 7 or greater suggests vascular dementia.
2. DEFINITION AND DIAGNOSTIC CRITERIA FOR VASCULAR DEMENTIA

- Diagnosis difficulties result not only from variability in clinical presentation but also from the frequency of mixed diseases. Recent studies with systematic neuropathological verification of a previously defined population have demonstrated that the frequency of mixed pathologies is usually around 60% [BO-34]. This high frequency probably reflects the later age of death (mean age around 85).

- Associated pathologies consist mainly of Alzheimer disease and to a lesser extent, Lewy body pathology.

- Reciprocally, around 39-48% of “Alzheimer disease brain” had associated vascular lesion [30,32,33]. An additive effect between pathologies has been shown [30,32,34].
In the last decade, the limitations and utility of the concept of VaD have been repeatedly disputed.

Recently, the term of "vascular cognitive impairment" was proposed to better account for the whole spectrum of cognitive alterations secondary to ischemic or hemorrhagic cerebral insults, which expand well beyond to dementia [5].

This approach is probably of crucial importance for prevention of VaD, which is detected only at the end stage of various progressive vascular disorders.

However, the framework of VaD still remains useful for clinical practice and the development of drugs.
3. CATEGORIES OF VASCULAR DEMENTIA

In clinical practice, the diagnosis of VaD is usually raised in the presence of a demented patient who has had a stroke or who has presented with cerebral lesions suggestive of a vascular origin on CT or MRI. The most sensitive technique for the diagnosis of these lesions is MRI.
3. CATEGORIES OF VASCULAR DEMENTIA

The lesions can be of various types:

- white matter changes, which are identified as hyperintense signals on T2-weighted MRI (or hypodensities on CT) in the white matter; these are presumably related to demyelination and axonal loss (also called leukoaraiosis) and are associated with diffuse small vessel diseases [36]
- “so-called” silent infarcts detected in the absence of stroke events, which are most often small in size (lacunar infarcts) and located in the white matter or subcortical gray matter [37]
- large subcortical or cortical ischemic lesions caused by the occlusion of large vessels
- micro-hemorrhages from rupture of small vessels, which are easily detected on specific MRI sequences [38]
- large hemorrhages, which most often have the same origin and a different distribution according to the underlying vessel disease.
3. CATEGORIES OF VASCULAR DEMENTIA

Types of brain lesions diagnosed using MRI
• The contribution of these different lesions will largely depend on their number, location, and on the presents of associated degenerative lesions.

• Classical categories of VaD include:
  1. single stroke dementia,
  2. multi-infarct dementia,
  3. subcortical ischemic VaD,
  4. dementia related to cerebral hemorrhages, and
  5. mixed dementia.

• A study with neuropathological analysis [39] showed that associated Alzheimer disease is more frequent in patients with a large vessel disease (which is usual in single stroke dementia).

• This implies that single stroke dementia is more frequently a mixed dementia. White matter abnormalities are usually the result of more or less complete ischemia, and a frequent question concerns the relation with cerebral amyloid angiopathy, which may be present in Alzheimer disease. A large study with neuropathological analysis showed that white matter ischemia and cortical microinfarcts were not related to Alzheimer pathology or to amyloid angiopathy [40].
3. CATEGORIES OF VASCULAR DEMENTIA

- Dementia may be observed in patients with isolated vascular lesions (hemorrhage or infarct) in the cortical or subcortical regions [41].

- However, such a diagnosis requires a detailed neuroradiological study to exclude associated small lesions and leukoaraiosis and to exclude other causes of dementia, particularly Alzheimer disease.
3.1. DEMENTIA IN PATIENTS WITH A SINGLE VASCULAR LESION OR SINGLE STROKE

3.1. A. Cortical stroke

- In the cortex, vascular lesions can cause dementia when they involve regions with heteromodal functions, particularly the limbic system or the cortical association areas.
- Isolated cortical infarctions causing dementia have been reported in three main locations:
  1. the angular gyrus (middle cerebral artery lower division),
  2. the inferomesial temporal lobe (posterior cerebral artery territory), and
  3. the mesial frontal lobe (anterior cerebral artery) [42,43].

All are responsible for anterograde amnesia.
The angular gyrus syndrome secondary to a lesion of the dominant hemisphere also includes:

- aphasic disturbances,
- constructional difficulties, and the
- Gerstmann tetrad (left-right disorientation, linger agnosia, dyscalculia, and dysgraphia).

In angular gyrus infarcts of the non-dominant hemisphere, spatial hemineglect and visuoconstructive disorders are associated with memory impairment [43,44].
3.1. DEMENTIA IN PATIENTS WITH A SINGLE VASCULAR LESION OR SINGLE STROKE

3.1. A. **Cortical stroke**

- In inferomesial temporal lobe infarctions, amnesia is caused by the resulting mediotemporal lesions and may be associated with language, visuospatial difficulties, and/or constructional apraxia according to the affected hemispheric side [45,46].

- Mesial frontal lobe infarcts mainly occur after a complicated rupture of an anterior communicating artery aneurysm [47,48].
3.1. DEMENTIA IN PATIENTS WITH A SINGLE VASCULAR LESION OR SINGLE STROKE

3.1. B. Subcortical stroke

- Isolated subcortical vascular lesions (mainly small deep infarcts) can lead to a dementia syndrome when they disrupt specific subcortical-cortical loops, which are crucial for the maintenance of the cortical functional integrity and finally for cognitive status [49].
- The main locations for a single small deep hemorrhage or ischemic lesion causing dementia are:
  a) the thalamus,
  b) genu of internal capsule, and
  c) possibly the caudate nucleus.
3.1. DEMENTIA IN PATIENTS WITH A SINGLE VASCULAR LESION OR SINGLE STROKE

3.1. B. Subcortical stroke

a). Thalamic infarctions

- Thalamic infarctions leading to dementia are mainly located either in the territory of the polar artery irrigating the anterior thalamus or in that of the paramedian arteries, which frequently arise from a common stem and irrigate in 50% of individuals both thalami and both sides of midbrain [50].

- Infarcts in the territory of the polar artery may induce:
  - executive disorders,
  - deficit of episodic memory [51],
  - are associated in left brain damage with aphasia that is close to the transcortical motor syndrome
  - in few cases, a total loss of psychic selfactivation has been reported [52].

- Patients with unilateral paramedian thalamic infarct usually present with:
  - an acute decrease of consciousness,
  - neuropsychological disturbances, and
  - abnormalities of vertical gaze [53].
3.1. DEMENTIA IN PATIENTS WITH A SINGLE VASCULAR LESION OR SINGLE STROKE

3.1. B. Subcortical stroke

a). Thalamic infarctions

- The cognitive alterations become evident with the resolution of consciousness impairment.
- Amnesia is sometimes prominent, leading to confabulations, and may be related to the lesion of the mamillothalamic tract.

- The cognitive impairment is more severe in the presence of bilateral paramedian thalamic-subthalamic infarcts responsible for amnesia associated with executive disorders such as abulia, aspontaneity, and inertia [52].

- The clinical presentation of thalamic hemorrhages is similar to that of thalamic infarcts and depends mainly on the size and location of the hematoma. Consequently, both anterolateral (corresponding to the territory of polar artery) and medial (corresponding to paramedian thalamic-subthalaric arteries) thalamic hemorrhages can cause a definite dementia syndrome [54].

- Baron et al. [49] confirmed by positron emission tomography (PET) that the cognitive impairment after unilateral thalamic lesion was correlated with ipsilateral cortical hypometabolism, thus supporting a depression of the cortical synaptic activity. These remote cortical effects might be related to the damage of the “non-specific” thalamic nuclei involved in the neocortical activation. This contrasts with vascular lesions of specific nuclei such as the ventro-postero-lateral nucleus, which spares the cognitive status [49,55].
3.1. B. Subcortical stroke

b). Capsular genu infarction

- **Capsular genu infarction on the left side** is another cause of “focal dementia”. Tatamichi et al. [56] have reported on four patients who had such a lesion with severe memory verbal loss associated with various cognitive deficits indicating dementia.
- They inferred that this lesion was responsible for cortical deactivation (mainly the frontal cortex) by interrupting the inferior and anterior thalamic peduncles [41,42].
- The persisting dementia syndrome after recovery is possibly favored by the presence of other old cerebral ischemic lesions [57].
3.1. DEMENTIA IN PATIENTS WITH A SINGLE VASCULAR LESION OR SINGLE STROKE

3.1. B. Subcortical stroke

c). Caudate nucleus

- **Isolated caudate vascular lesions** may also be responsible for behavioral or cognitive disturbances [58]. Caplan et al. [59] reported neuropsychological alterations in 14 of 18 patients (7800) with unilateral infarcts. The clinical presentation included various neuropsychological symptoms with *prominent disorders of executive functions*:
  - reduced activity and abulia or affective symptoms (depression) with psychotic features (dorsolateral caudate),
  - restlessness,
  - hyperactivity, and
  - decreased attention (ventromedial caudate) [60].

- Cognitive testing can reveal memory disturbances, sometimes with poor recall of long-term memory [61], most often associated with abnormalities in executive functions and attention and in few cases with **aphasic difficulties** *(left caudate infarcts)* or **hemineglect** *(right caudate infarcts)* [59,60]. Godefroy et al. [62] did not observe dementia but only mild cognitive alterations in patients with pure unilateral lenticulostriate infarcts, including caudate infarcts.

- Dementia was only observed in patients with multiple infarcts (particularly lacunes) and/or extensive leukoaraiosis, which was noticeably underestimated on CT. Therefore, pure caudate stroke induces severe cognitive deficit matching dementia criteria in rare cases [63] and this prompts the search for associated Alzheimer disease.
3.2. DEMENTIA SECONDARY TO MULTIPLE CORTICAL AND SUBCORTICAL ISCHEMIC LESIONS ("MULTI-INFARCT DEMENTIA")

• In the presence of severe vascular disorders leading to *repeated cortical and subcortical infarctions*, the increased risk of dementia with the accumulation of lesions is obvious.

• There is no specific criterion to confirm the vascular origin of dementia in a given patient and because of the high frequency of both Alzheimer disease and vascular disorders with aging.

• During the last decades, some authors have reported that the abrupt onset of dementia, a history of stroke, the presence of focal symptoms or focal signs with the presence of isolated or multiple CT low-density areas were the most discriminating parameters suggesting a vascular origin [64].

• However, Chui et al. [65] showed that scales based on these clinical features were fairly sensitive and specific (70-80%) in differentiating pure Alzheimer disease and multi-infarct dementia but insensitive to the presence of mixed dementia (1730%).

• Another debated issue has been the role played by the location versus the volume of the lesions in the dementia syndrome. This was recently settled by Zekry et al. [66], who demonstrated in patients with pure VaD and mixed dementia that the location of infarctions was the main contributor to the variability of the Mini Mental Status Examination (MMSE) score (at the equal level with degenerative lesions in mixed dementia) while volume of lesions had an insignificant role.

• The location of cerebral tissue lesions in strategic cortical or subcortical areas involved in the higher cortical functions (those entering in the definition of dementia) is finally *the most important factor leading to dementia in vascular disorders*. 
3.3. DEMENTIA SECONDARY TO MULTIPLE DEEP INFARCTS AND LEUKOENCEPHALOPATHY IN SMALL CEREBRAL ARTERY DISEASES

3.3.1. Binswanger disease

3.3.2. CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy)

3.3.3. Other arteriolopathies leading to small deep infarcts and leukoencephalopathy
3.3.1. **Binswanger disease**

- In 1894, Otto Binswanger described “encephalitis subcorticalis chronical progressiva”, a condition characterized by dementia and recurrent stroke, with white matter atrophy at pathological examination.

- Binswanger's disease (BD), also called **subcortical vascular dementia**, is a type of dementia caused by widespread, microscopic areas of damage to the deep layers of white matter in the brain. The damage is the result of the thickening and narrowing (atherosclerosis) of arteries that feed the subcortical areas of the brain. Atherosclerosis (commonly known as "hardening of the arteries") is a systemic process that affects blood vessels throughout the body.

- It begins late in the fourth decade of life and increases in severity with age. As the arteries become more and more narrowed, the blood supplied by those arteries decreases and brain tissue dies.

- A characteristic pattern of BD-damaged brain tissue can be seen with modern brain imaging techniques such as CT scans or magnetic resonance imaging (MRI).
3.3. DEMENTIA SECONDARY TO MULTIPLE DEEP INFARCTS AND LEUKOENCEPHALOPATHY IN SMALL CEREBRAL ARTERY DISEASES

3.3.1. **Binswanger disease**

- The symptoms associated with BD are related to the disruption of subcortical neural circuits that control what neuroscientists call executive cognitive functioning:
  - short-term memory,
  - organization,
  - mood,
  - the regulation of attention,
  - the ability to act or make decisions, and
  - appropriate behavior.
3.3. DEMENTIA SECONDARY TO MULTIPLE DEEP INFARCTS AND LEUKOENCEPHALOPATHY IN SMALL CEREBRAL ARTERY DISEASES

3.3.1. Binswanger disease

- The most characteristic feature of BD is psychomotor slowness - an increase in the length of time it takes. Other symptoms include forgetfulness (but not as severe as the forgetfulness of Alzheimer's disease), changes in speech, an unsteady gait, clumsiness or frequent falls, changes in personality or mood (most likely in the form of apathy, irritability, and depression), and urinary symptoms that aren't caused by urological disease.

- Brain imaging, which reveals the characteristic brain lesions of BD, is essential for a positive diagnosis.

- Finally, Binswanger disease should not be considered as a pathophysiological entity but rather as the final stage of a long history of small artery disease related to hypertension.
3.3. DEMENTIA SECONDARY TO MULTIPLE DEEP INFARCTS AND LEUKOENCEPHALOPATHY IN SMALL CEREBRAL ARTERY DISEASES

3.3.2. CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy)

- CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) was identified in 1993 as a new cause of “pure vascular dementia.”
- It is also considered as a unique model for subcortical ischemic VaD.
- The disease is an **autosomal dominant arteriopathy** secondary to NOTCH3 mutations on chromosome 19 [74].
- **Histological** studies in CADASIL showed a widespread palor of white matter and multiple small infarcts in the white matter and basal ganglia [75,76]. Electron microscopy studies revealed that the media of small white matter and leptomeningeal arteries is thickened by a granular, eosinophilic, and non-amyloid material of undetermined origin adjacent to the smooth muscle cells. These ultrastructural wall abnormalities have been observed in other arteries, particularly in muscular and skin vessels.
3.3. DEMENTIA SECONDARY TO MULTIPLE DEEP INFARCTS AND LEUKOENCEPHALOPATHY IN SMALL CEREBRAL ARTERY DISEASES

3.3.2. CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy)

Classical CADASIL in the 6th decade

78 year old paucisymptomatic individual with a NOTCH3 mutation

73 year old asymptomatic individual with a NOTCH3 mutation (MRI scan made at 58 years of age)

Axial FLAIR (a, b & c) and T2 weighted (d) Brain MRI from patients with CADASIL
The most common symptoms of CADASIL include:

✓ **Migraine with aura**: a migraine is a vascular headache resulting from changes in the sizes of the arteries in the brain. An aura refers to an abnormal sensation that the migraine is going to occur.

✓ **Psychiatric disturbance**: any number of mood disorders can occur as a result of CADASIL, including depression.

✓ **Ischemic episodes**: Loss of blood flow to the brain, causing symptoms similar to those of a stroke.

✓ **Cognitive deficits**: these might include deficits in memory, attention, multi-tasking and personality; the cognitive abilities generally decline as the disease worsens.

✓ **Progressive memory loss** and **dementia**

✓ **Multiple strokes** leading to hemiparesis (paralysis of one side of the body), walking difficulty and visual impairment.

✓ Rarely, epileptic seizures
3.3. DEMENTIA SECONDARY TO MULTIPLE DEEP INFARCTS AND LEUKOENCEPHALOPATHY IN SMALL CEREBRAL ARTERY DISEASES

3.3.2. CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy)

- The disease can start with attacks of migraine with aura, which are observed in one-third of symptomatic patients with CADASIL, at a mean age of 30 years [77,78].
- The most frequent clinical manifestations are subcortical transient ischemic attacks or strokes, occurring between 40 and 50 years of age [77,78].
- **Cognitive impairment** is the second most frequent clinical manifestation of CADASIL. It can be associated with mood disturbances.
- Symptomatic patients can remain for several years without any neuropsychological decline [79]. However, signs of cognitive impairment are often detected early in executive function and processing speed in symptomatic subjects when using dedicated tests such as the Wisconsin Card Sorting and the Trail Making tests [80]. Executive dysfunction was present in all individuals aged 35-50 years in a series of 42 symptomatic patients. [81]
3.3. DEMENTIA SECONDARY TO MULTIPLE DEEP INFARCTS AND LEUKOENCEPHALOPATHY IN SMALL CEREBRAL ARTERY DISEASES

3.3.2. CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy)

- It is often associated later with alterations in attention and memory [80,81].
- Apathy characterized by a lack of motivation associated with a reduction in voluntary behavior is a frequent clinical manifestation of the disease associated with cognitive impairment. It is present in approximately 4000 of patients, independently of depression [83].
- With aging, the cognitive decline becomes more extensive, with a progressive appearance of alterations in instrumental activities, verbal or visual memory, language, reasoning, and visuospatial abilities [81]. There is, however, a relative preservation of recognition and semantic memory, and severe aphasia, apraxia, or agnosia is rare [81,84].
- The profile of memory deficit is usually distinct from that of dementias primarily involving the mesiotemporal temporal cortex, such as Alzheimer disease. This is illustrated by procedures such as those used in the Grober and Buschke Test (Free and Cued Selective Reminding Test).
- Dementia is observed in one-third of symptomatic patients at the late stage of the disorder. The frequency of dementia increases considerably with age:
  - approximately 60% of patients older than 60 years are demented and
  - more than 80% of deceased subjects were reported to be demented before death.
3.3. DEMENTIA SECONDARY TO MULTIPLE DEEP INFARCTS AND LEUKOENCEPHALOPATHY IN SMALL CEREBRAL ARTERY DISEASES

3.3.3. Other arteriolopathies leading to small deep infarcts and leukoencephalopathy

• Other rare specific vascular conditions leading to multiple small brain infarcts have been recognized as possible causes of VaD. In most of them, the exact origin of the vessel disease remains to be ascertained. In few isolated cases with extensive pathological data, the clinical and pathological features were close to that of Binswanger disease except for the lack of hypertension and the younger age of onset [110,111] or because of distinct ultrastructural wall abnormalities involving both capillaries, arterioles, and venules [112]. Hereditary conditions leading to VaD distinct from CADASIL have been also reported.

• The disease known as CARASIL (cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy) has been related to mutations of HTRA I, encoding a serine protease (HtrA serine protease 1) that represses signaling by members of the transforming growth factor-beta, which are involved in vessel wall fibrosis [115].

• Histopathologically, CARASIL is characterized by intense arteriosclerosis, mainly in the small penetrating arteries, without granular osmiophilic materials or amyloid deposition.
3.4. DEMENTIA RELATED TO MULTIPLE BRAIN HEMORRHAGES AND AMYLOID ANGIOPATHIES

- The inclusion or exclusion of cerebral hemorrhages (intracerebral and subarachnoid) as classical causes of VaD is a matter of debate. Some authors have proposed that these should be considered separately since they usually present primarily as major strokes, with neurological deficit overshadowing the cognitive impairment [121,122]. Nevertheless, in amyloid angiopathy, dementia is a prominent symptom that sometimes occurs progressively.

- **Amyloid angiopathy** is only one aspect of cerebral diseases with amyloid deposits [123]. Amyloid is merely a descriptive term for proteins with particular physical characteristics [124] that can be present in the neurons as neurofibrillary tangles, in the neuropil as plaques, or in the vessel wall as amyloid angiopathy. Various chemical types of amyloid deposition have been recognized: B-amyloid A4 (AB), cystatin C, transthyretin, or prion protease-resistant protein. Mutations of protease-resistant protein are responsible for the Creutzfeldt-Jakob disease and the Gerstmann-Straussler syndrome, which are clearly distinct from VaD [123]. Conversely mutations affecting AB, cystatin C, or transthyretin induce amyloid angiopathies that lead to dementia [125,126].
3.4. DEMENTIA RELATED TO MULTIPLE BRAIN HEMORRHAGES AND AMYLOID ANGIOPATHIES

From: Herzig, Brain Pathology 2006
Most patients with amyloid angiopathy are usually sporadic and more than 40% are associated with Alzheimer disease [127]. While the 84 allele of apolipoprotein E has been identified as a risk factor for Alzheimer disease by promoting the aggregation and deposition of AB within the cortex [128], the E2 allele seems to play a major role in the deposition of AB in the vascular wall, leading to amyloid angiopathy and hemorrhages [126,129].

The location of cerebral hemorrhages is probably critical in the occurrence of cognitive impairment. Elsewhere, associated lesions such as small silent infarcts in cortical watershed areas [130], white matter lesions, and/or subcortical infarcts also related to amyloid angiopathy may participate in the alteration of the cognitive status.
3.5. DEMENTIA RELATED TO HEMODYNAMIC MECHANISMS

• **Hypoperfusion secondary to carotid diseases** is a very rare cause of “vascular dementia.” Unilateral or bilateral occlusion of carotid arteries is the most common precipitating factor [42]. Hemodynamic failure in the frontal borderzone supplied by the distal and most pial branches of the middle and anterior cerebral arteries can lead to ischemic lesions at distance from the sylvian area.

• **The clinical presentation** often includes only aphasia, apraxia, or hemineglect without prominent motor deficit [136]. In most cases, pathological examination reveals widespread or multifocal infarction in regions including the association areas of the anterior and posterior cerebrum.

• Chronic ischemia without infarction in the carotid territory is an exceptional cause of dementia.

• Rarely, the cognitive alteration been attributed to a “misery perfusion” in PET investigations [137]. This type of dementia is reversible after correction of the hemodynamic deficit. In one documented case, extraintracranial arterial bypass surgery was efficient in improving the cognitive status [137].
4. ASSESSMENT OF VASCULAR DEMENTIA

- The examination of a patient with VaD should include the assessment of the underlying cerebrovascular disease, the complete evaluation of the neurological and neuropsychological deficits, and an estimation of the rate of functional decline.
All causes of stroke can be responsible for VaD:

• **Large artery atherosclerosis** is a main cause of artery-to-artery embolism and thrombosis leading to cortical and subcortical infarcts.

• Heart disease, the most common being **atrial fibrillation**, is the source of small or large subcortical or cortical infarcts.

• Small artery disease changes autoregulation of perforating vessels and promotes small deep infarcts in basal ganglia, with leukoaraiosis.

• Some specific **vasculopathies**, inflammatory or not, including giant cell arteritis, Takayasu arteritis, isolated angiitis, and those connected with systemic diseases, such as Sjogren syndrome or systemic lupus erythematosus, can lead to multiple and widespread small infarcts, resulting in cognitive impairment.

• **Noninflammatory arteriopathies** such as fibromuscular dysplasia or moyo-moya disease can also cause VaD through multiple ischemic or hemorrhagic lesions.

• **Cerebral venous thrombosis** is another potential cause of ischemic and/or hemorrhagic brain insults.

• **Hematological factors** such as antiphospholipid antibodies increase the risk of thrombosis or polycythemia, causing repeated ischemic lesions or a “hyperviscosity induced dementia” and should also be considered as potential causes of VaD. Obviously, this listing cannot be exhaustive.
4. ASSESSMENT OF VASCULAR DEMENTIA

- In presence of VaD, the first step will consist in analyzing the cerebral tissue lesions based on imaging data.
- **Cerebral MRI** is the method of choice to assess the spectrum of cerebral lesions in patients with VaD. Multiple MRI sequences are necessary for this purpose and should include T1-weighted images, T2 or FLAIR images, T2* or gradient-echo images, and magnetic resonance angiography. Diffusion-weighted MRI is particularly useful to detect recent ischemic insults (less than 10 days).
- The assessment of tissue lesions on MRI will concern
  1. the presence of **ischemic lesions** (recent or old),
  2. the presence or absence of **hemorrhagic lesions** (recent or old; best evaluated on gradient-echo images).
  3. **the size of lesions** (large territorial infarction or small deep infarcts; recent large hematoma or microbleeds),
  4. **the location** of lesions in strategic areas (heteromodal cortices, mesio-temporal or frontal cortex, internal thalamus or genu of internal capsule), and
  5. the presence and extent of **white matter changes** and location of these corresponding signal changes.
- According to the location, number, and type of these different lesions, the vascular mechanism can be suspected in the vast majority of cases. Thereafter, the work-up is identical to that performed in stroke patients: electrocardiography, cardiac echography, ultrasound examination of cervical arteries, blood cell count, lipid profile, and erythrocyte sedimentation rate. Other examinations such as the analysis of cerebrospinal fluid, coagulation factors, or genetic testing will be considered only in few cases and according to the context (e.g. familial disorder, cancer, other peripheral vascular events).
5. TREATMENT

- At the present time, no specific tool is available to assess the risk for vascular dementia or recurrent stroke.
- Meanwhile, the Framingham Stroke Risk Profile is a useful tool to estimate the 10-years risk stroke for men and women aged 55-80 years old, based on:
  - age
  - systolic blood pressure
  - diabetes
  - smoking
  - cardiovascular disease
  - atrial fibrillation
  - left ventricular hypertrophy

(D’Agostino et al, 1994; Wolf et al., 1991)
# 5. TREATMENT

## Table. Risk Factors for Stroke

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Sex-Specific Risk Factors</th>
<th>Risk Factors That Are Stronger or More Prevalent in Women</th>
<th>Risk Factors That Are Similar in Men and Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy, preeclampsia, or gestational diabetes</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral contraceptive or postmenopausal hormone use</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Migraine headache</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>with aura</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical inactivity, obesity, or unhealthy</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Prior cardiovascular disease</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>The metabolic syndrome</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Psychosocial stress</td>
<td></td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>
5. TREATMENT

5.1. Prevention of vascular dementia

• There are different observational studies showing that dementia (as observed in stroke) is more frequent in the presence of vascular risk factors such as carotid atherosclerosis, cardiac pathology, hypertension, and diabetes and is less frequent with moderate alcohol intake.

• However, only recent interventional studies have demonstrated that manipulation of vascular risk factors is actually effective in reducing the risk of dementia. In the Syst-Eur and PROGRESS trials, a significant reduction in the risk of dementia was detected with a decrease of blood pressure (from 5 to 10 mmHg). The Syst-Eur trial was recently updated for the incidence of dementia in patients treated since randomization (calcium channel blocker versus placebo) and showed a reduction of dementia from 7.4 to 3.3 cases per 1000 patient-years with the antihypertensive drug, with a reduction of the incidence of both Alzheimer disease and VaD [171,172]. In the PROGRESS trial, which examined the balance of benefit and risk with perindopril (angiotensin-converting enzyme inhibitor) with and without indapamide (diuretic) versus placebo in patients with a history of stroke, the active treatment was also found to decrease by 19% the risk of cognitive decline in the whole population and by 45% in subjects with recurrent stroke [173]. These results strongly support the contention that the reduction of blood pressure is crucial to reduce the risk of dementia in general and particularly of VaD.

• At the individual level, the prevention of VaD should be considered in patients with transient ischemic attack or stroke, who usually have a complete work-up for their underlying vascular disease, but may also be considered in future for patients with newly identified risk factors, as detected with imaging, such as silent white matter lesions and silent cerebral infarcts.
5. TREATMENT

5.2. Improvement of cognitive performance in vascular dementia

• Several randomized controlled trials have examined the efficacy of cholinesterase inhibitors (donepezil, rivastigmine, and galantamine) and memantine in VaD.

• Most trials have included patients aged 40 to 90 years with stabilized vascular disease for 6 months, probable or possible VaD using NINDS-AIREN criteria (others use more restrictive criteria such as probable VaD plus abnormal Hachinski score), imaging evidence of vascular lesions (which was mainly from small vessel disease), and MMSE scores >9 [174]. The primary endpoint was assessed after 24 to 28 weeks, often with the Alzheimer Disease Assessment Scale cognitive subscale (ADAS-Cog; or Vascular ADAS-Cog) and the Clinician’s Interview Based Impression Of Change (CIBIC-plus) [175178].

• Overall the cholinesterase inhibitors provided a significant improvement of small magnitude for cognitive and behavioral assessment without benefit of clinical global measure. For that reason, they are not approved in most countries, although this is the first time a pharmacological treatment has been shown to improve post-stroke cognitive deficit.
5. TREATMENT

5.2. Improvement of cognitive performance in vascular dementia

<table>
<thead>
<tr>
<th>Medication</th>
<th>Initial Dose</th>
<th>Titration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donepezil hydrochloride (Aricept) tablets, ODT, OS</td>
<td>5 mg/day × 4-6 wk</td>
<td>Increase to 10 mg qd (max)</td>
</tr>
<tr>
<td>Galantamine hydrobromide IR (Razadyne) tablets, OS</td>
<td>4 mg bid × 4 wk</td>
<td>Increase to 8 mg bid × 4 wk; then to 12 mg bid × 4 wk; max 32 mg/daya</td>
</tr>
<tr>
<td>Galantamine ER (Razadyne ER) capsulesa</td>
<td>8 mg/day × 4 wk</td>
<td>Increase to 16 mg/day × 4 wk; max 24 mg/day × 4 wk</td>
</tr>
<tr>
<td>Rivastigmine tartrate capsules, OS</td>
<td>1.5 mg bid × 2 wk</td>
<td>Increase to 3 mg bid × 2 wk; then to 4.5 mg bid × 2 wk; max 6 mg bid</td>
</tr>
<tr>
<td>Rivastigmine transdermal system (Exelon Patch)</td>
<td>4.6 mg/day × 4 wk</td>
<td>Increase to 9.5 mg/day (max)</td>
</tr>
<tr>
<td>Memantine (Namenda) tablets, OS</td>
<td>5 mg qd × 1 wk</td>
<td>Increase to 5 mg bid × 1 wk; then to 10 mg qam + 5 mg qpm × 1 wk; max 10 mg bidb</td>
</tr>
</tbody>
</table>

* In moderate renal or hepatic impairment, max recommended dose is 16 mg/day. Galantamine is not recommended when CrCl is <9 mL/min or in severe hepatic impairment.

a In patients with CrCl 5-29 mL/min, max recommended dose is 5 mg bid.

b CrCl: creatinine clearance; ER: extended-release; IR: immediate-release; max: maximum; ODT: orally disintegrating tablets; OS: oral solution.

Source: Reference 24.
5. TREATMENT

5.2. Improvement of cognitive performance in vascular dementia

- Cholinesterase inhibitors and memantine are frequently used in patients with Alzheimer disease and stroke (either diagnosed clinically or by imaging). A first trial including differing populations suggests that it might benefit such patients [180]. However, the benefit of such strategy in mixed dementia remains to be proven by additional trials focusing on such a population.

- When VaD is diagnosed, vascular risk factors, if still present, are treated.

- In addition, if VaD results from ischemic stroke, an antiplatelet agent is usually given. This strategy is logical considering evidence for benefit from studies performed in nondemented patients, although no randomized controlled trial has adequately addressed this point yet [181,182]. There is a general professional consensus to maintain this approach but to consider that adequate trials are urgently needed.

- Other treatments such as propentofylline [183], vinpocetine [184], nimodipine [185], serotonine reuptake inhibitor, and cognitive training [186] require additional controlled trials before drawing any firm conclusions. Serotonergic antidepressants should also be assessed as several small randomized trials suggest that they may favor improvement of post-stroke motor deficit [187].
Thank you!