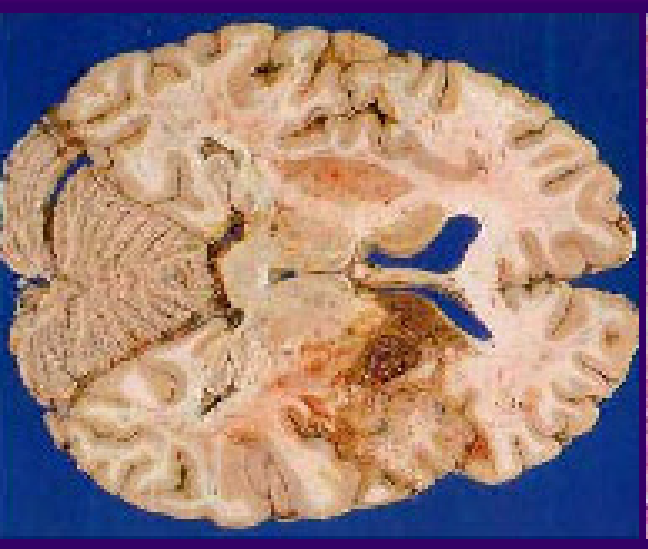
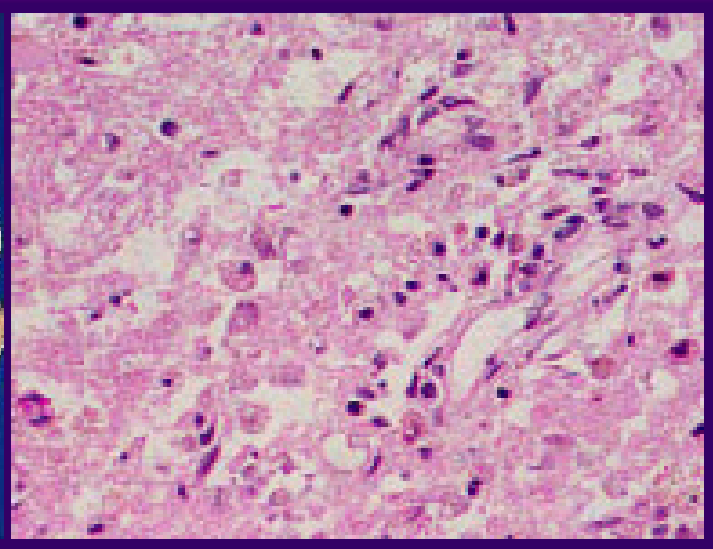
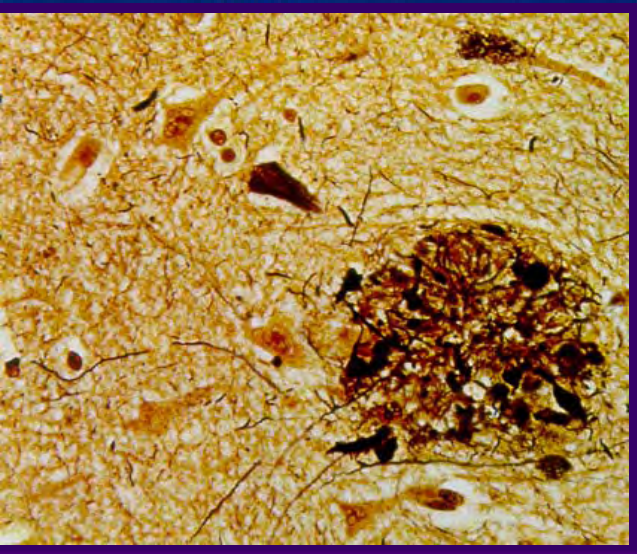
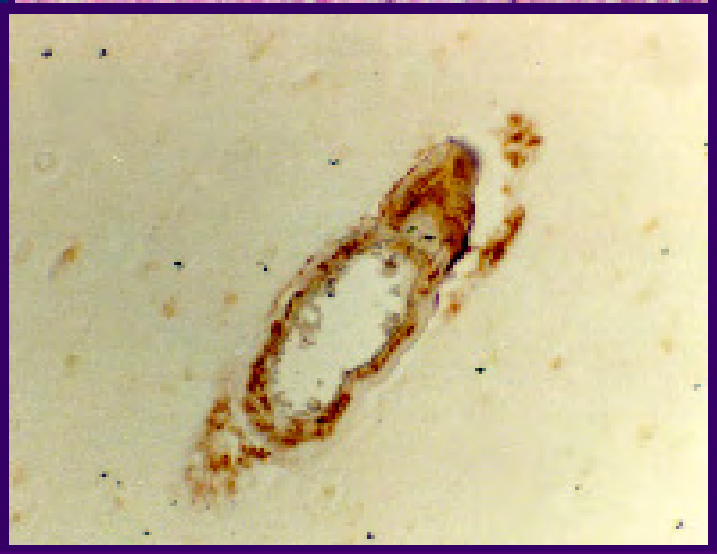
Pathology and Pathophysiology of Vascular and Mixed Dementia









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Cognitive dysfunctions caused by cerebral lesions due to vascular/ischemic pathology

Synonyms:

- old: Arteriosclerotic dementia - "inaccurate and misleading"
- Multi-infarct dementia (Hachinski et al. 1974) – only subtype
- Dementia associated with stroke (Gorelick, 1997
- Vascular dementia (Esiri et al.,1997; Markesbery 1998)
- Cerebrovascular dementia (Erkinjuntti, 1999)
- Ischemic-vascular dementia (Vinters et al., 2000)
- Vascular-ischemic dementia (Jellinger, 2002)
- Vascular cognitive impairment (Bowler & Hachinski, 1999; 2003)

Hachinski score

Clinical feature	Score
Abrupt onset	2
Stepwise deterioration	1
Fluctuating course	2
Nocturnal confusion	1
Relative preservation of personality	1
Depression	1
Somatic complaints	1
Emotional incontinence	1
History of hypertension	1
History of stroke	2
Clinical evidence of atherosclerosis	1
Focal neurologic symptoms	2
Focal neurologic signs	2

from Hachinski et al, Arch Neurol 32; 1975: 632

A total score of 4 or less is suggestive of a degenerative cause of dementia such as Alzheimer's disease

A score of 7 or more is suggestive of vascular dementia

SCADDTC and NINDS-AIREN criteria of vascular-ischemic dementia (VID)

Possible VID:

1) Clinical criteria of dementia with one or more cerebral infarcts

2a) History (one infarct with dementia in timely relationship)

2b) Binswanger's syndrome with early urinary incontinence, gait disorders, vascular risk factors, white matter lesions CCR / MRI

Probable VID:

1) All clinical signs of dementia

2) Two ore more cerebral infarcts (history, clinic, imaging) or one infarct followed by proven dementia

3) Imaging signs of at least one extracerebellar infarct

Proven VID:

a) Clinically proven dementia

b) Pathological demonstration of multiple cerebrovascular lesions

Mixed type dementia

Combination of degenerative (Alzheimer) and vascular dementia

Comparison of clinical criteria for vascular dementia (VaD)

I.

Criteria	Definition of dementia		CVD	Included mechanisms		
	Memory impairment	Cognitive		AI	CI	H
Hachinski ischemic score (1975)	NS	NS	Ascl	Yes	No	No
DSM-IV (1994)	Yes	One other	NS	Yes	NS	Yes
NINDS-AIREN probable VaD (Roman et al 1992)	Yes	Two others	NS	Yes	NS	Yes
ADDTC (Chui et al 1992)	±	Not limited to single category	NS	Yes	Yes	No

AI, acute ischemia; CI, chronic ischemia; H, hemorrhage; NS, not specified; ±, supportive for diagnosis

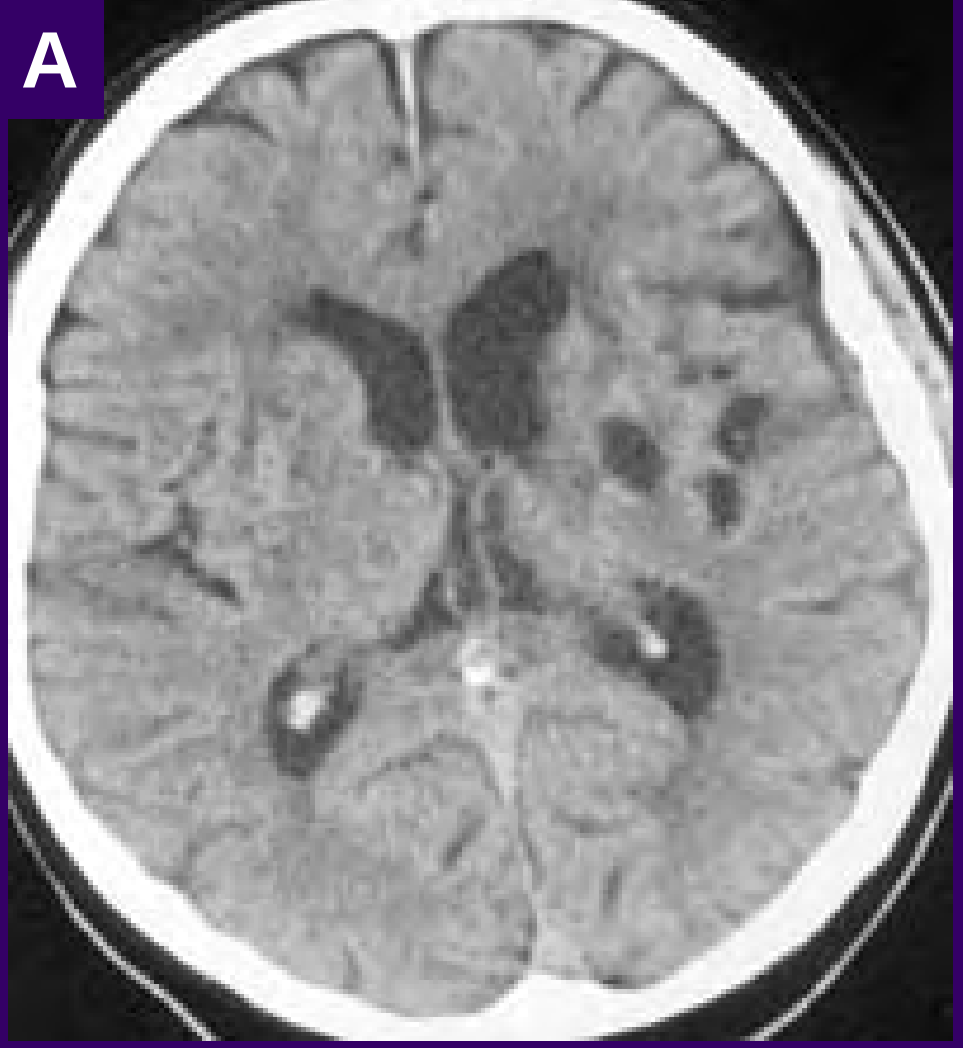
Comparison of clinical criteria for vascular dementia (VaD)

II.

Criteria	Excluded mechanisms	Neurol. examin.	Structural neuroimag.	Causal relationship
Hachinski ischemic score (1975)	None	± Focal signs	No	No
DSM-IV (1994)	Delirium	± Focal signs	±	Yes, by clinical judgement
NINDS-AIREN probable VaD (Roman et al 1992)	Delirium, aphasia, psychosis, Alzheimer or other brain disease	Focal signs	Yes (probable VaD) No (possible VaD)	Yes (probable VaD: within 3 mo, abrupt onset or stepwise progression) No (possible VaD)
ADDTC (Chui et al 1992)	Delirium	NS	Yes (probable or possible VaD)	± (Probable VaD: temporal relation for single lesion)

AI, acute ischemia; CI, chronic ischemia; H, hemorrhage; NS, not specified; ±, supportive for diagnosis

A



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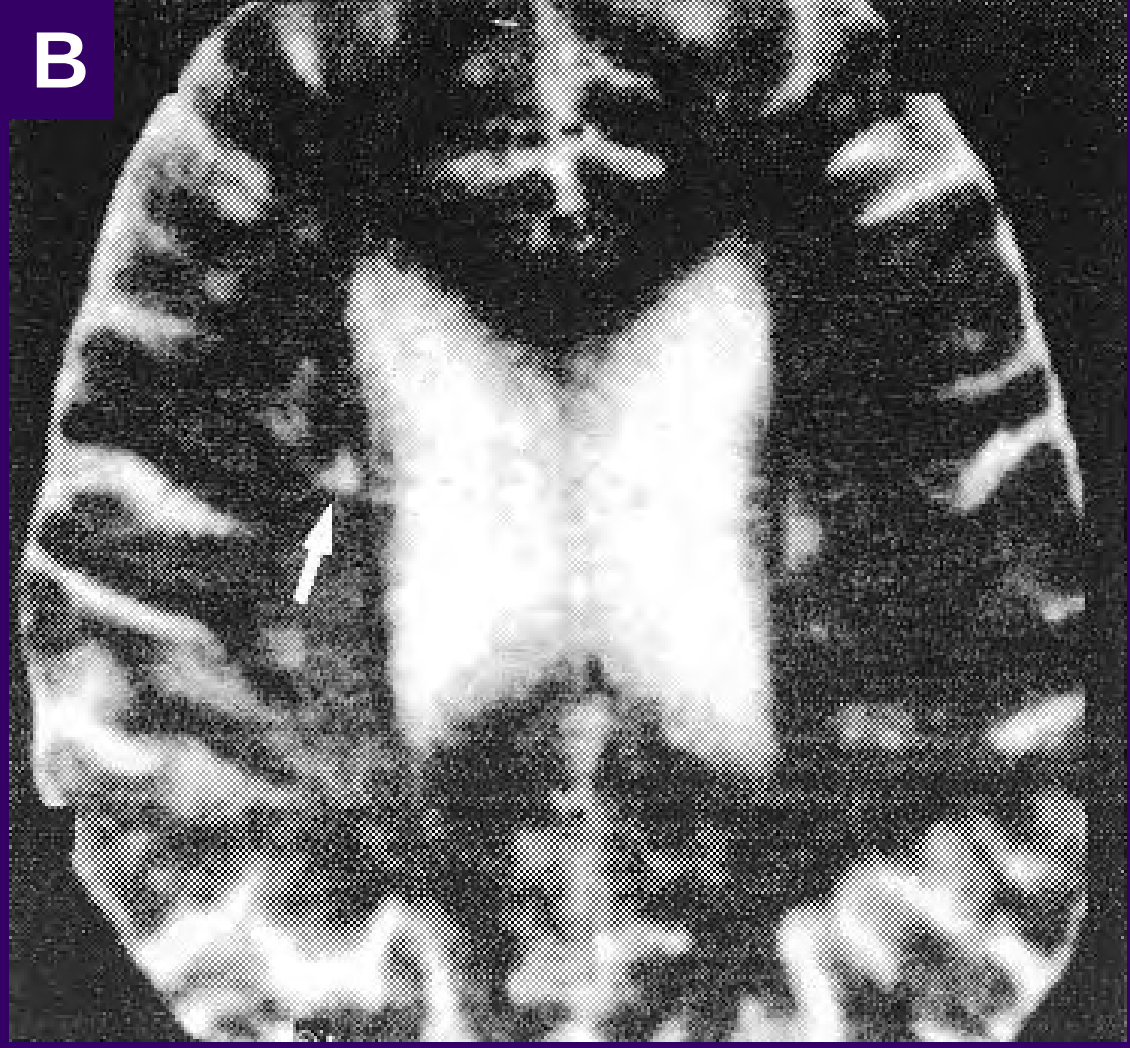

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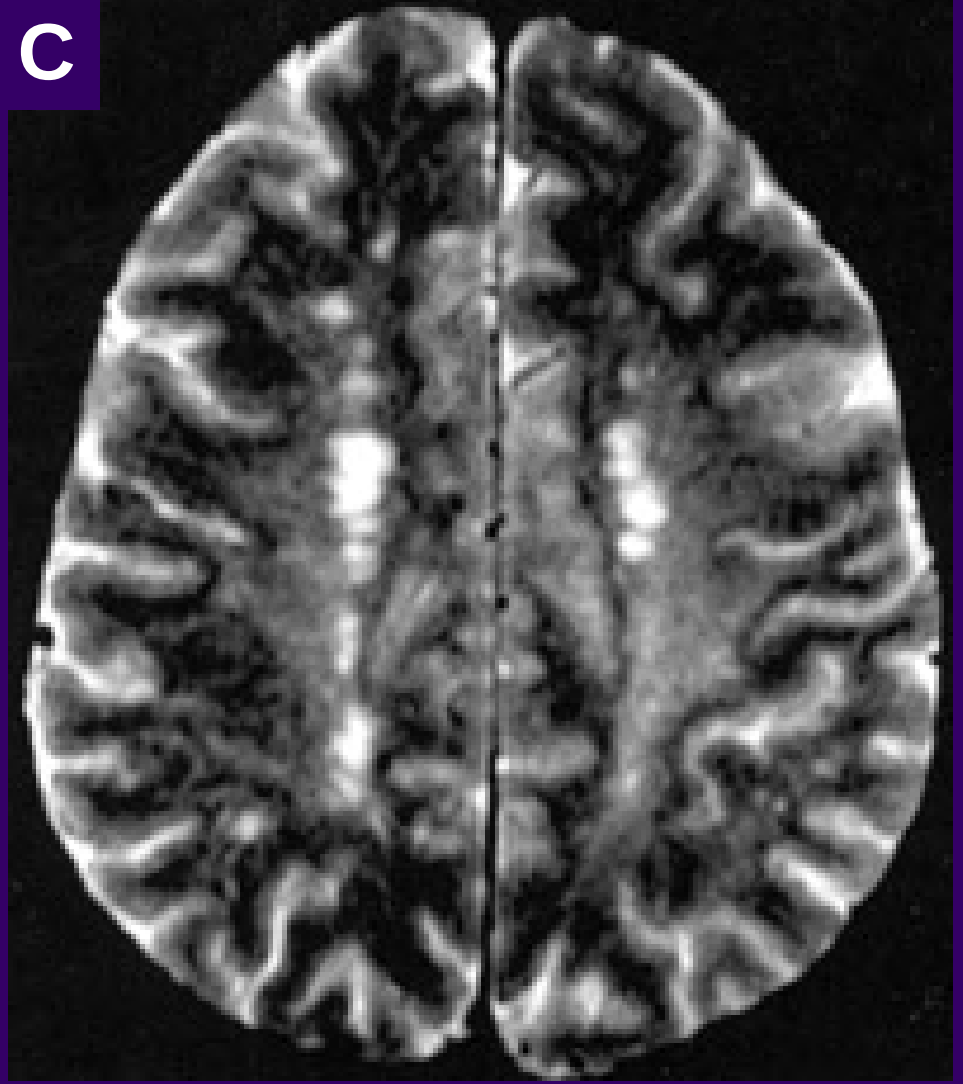

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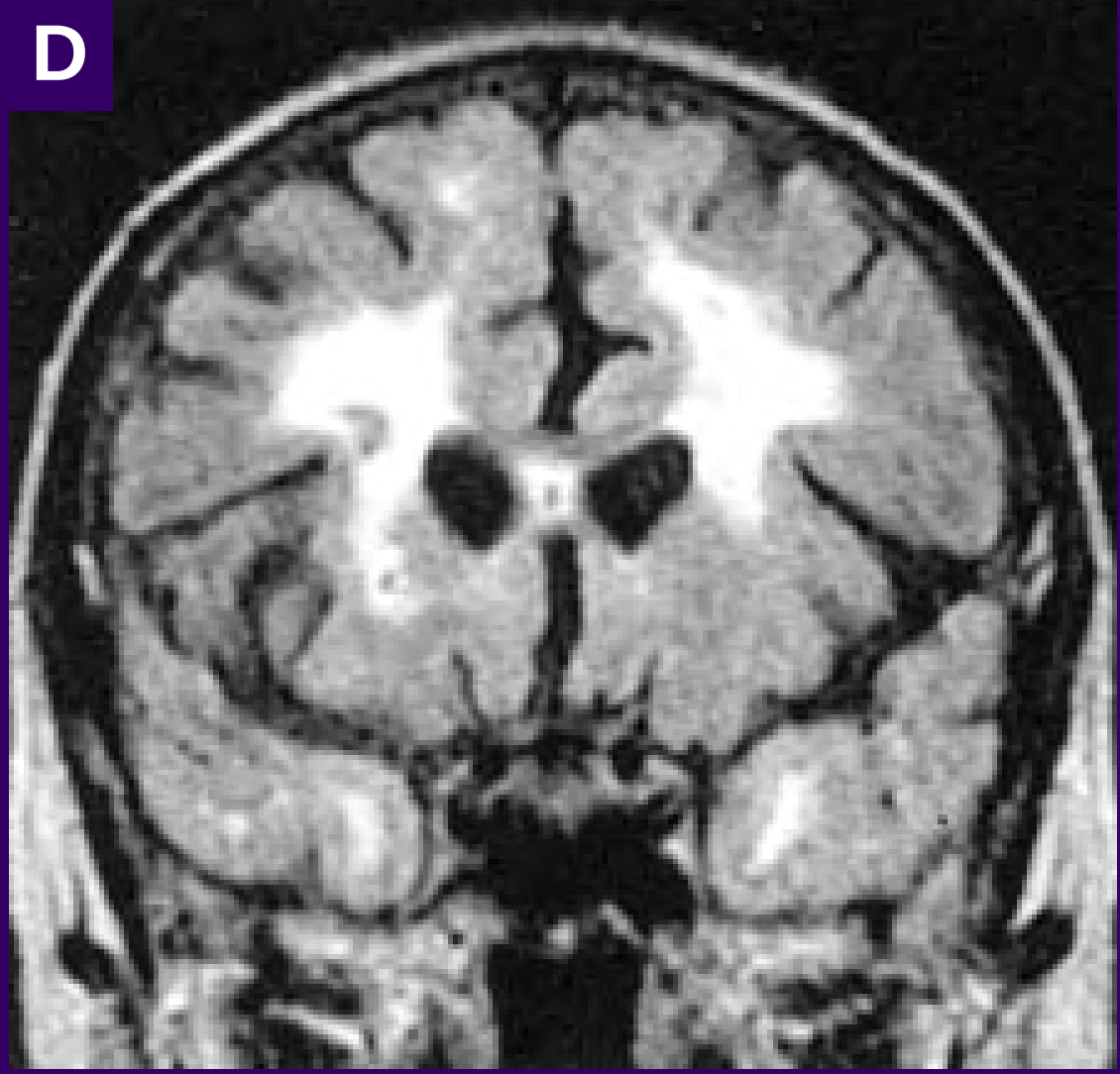


Major cerebrovascular lesions associated with cognitive impairment

1. Gross large infarcts in supply territories of large cerebral arteries, in particular MCA, MCA+PCA, unilateral or bilateral
2. Lacunes (lesions 0.5-15 mm (∅) and multiple microinfarcts or small hemorrhages in basal ganglia, thalamus, hippocampus, basal forebrain ("strategic infarct dementia")
3. Multiple microinfarcts/scars in cortical border zones ("granular cortical atrophy") - rare
4. Pseudolaminar cortical necrosis (mainly arterial border zones)
5. Hippocampal sclerosis
6. White matter lesions/leukoaraiosis/Binswanger disease
7. Combined cerebrovascular lesions

Dementia associated with cerebrovascular disease

A. Multifocal / Diffuse Disease: (Vinters et al, JNEN 59, 2000)

1. Multiple atherosclerotic/watershed infarcts (large artery/borderzone territories)
2. Anti-phospholipid-related ischemia
3. "Granular atrophy" of cortex (multifocal cortical microinfarcts)
4. Multiple lacunar infarcts (due to microvascular disease)
5. Binswanger subcort. leukoencephalopathy (BSLE) (Chr.4 ??)
6. CADASIL (related to NOTCH 3 mutations)
7. Angiitis (PCNSA, granulomatous angiitis; some linked to CAA)
8. Cerebral amyloid angiopathy - Familial forms including Dutch, Icelandic, British
9. Other angiopathies (Fibromuscular dysplasia, Moyamoya)
10. Cortical laminar necrosis (post-cardiac arrest, hypotension)
11. Extreme enlargement of brain perivascular spaces

Dementia associated with cerebrovascular disease

(Vinters et al, JNEN 59, 2000)

B. Focal Disease/Strategically Placed Infarcts:

1. Mesial temporal (including hippocampal) infarcts/ischemia/sclerosis
2. Caudate and thalamic infarcts (dorsomedial nucleus: bilateral damage)
3. Fronto-cingulate infarcts (anterior cerebral artery territory)
4. Angular gyrus infarct (dominant cerebral hemisphere)

Pathology of vascular dementia

Small vessel disease

- Ischemic white matter degeneration
- Cribriform atrophy of white matter
- Lacunar infarction in subcortical nuclei and white matter
- Granular atrophy of cortex

Large vessel disease

- Very extensive or multifocal infarction (multi-infarct dementia)
- Critically sited infarcts.

Hypoperfusion lesions

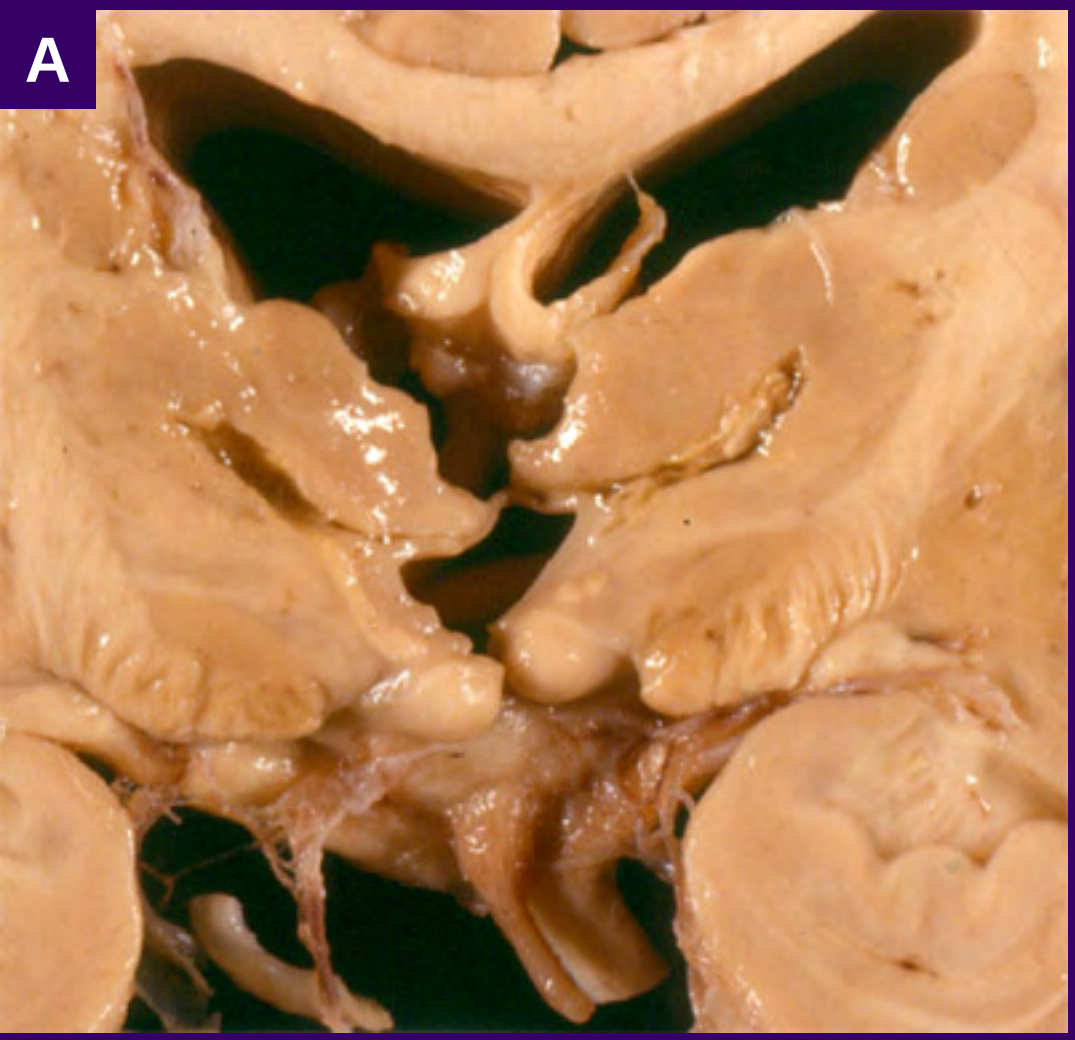
- Hippocampal sclerosis
- Laminar cortical necrosis

Rare local vascular disorders

- CADASIL
- Cerebral amyloidosis
- Cerebral vasculitis
- Antiphospholipid antibody syndrome

Subtypes of Vascular Dementia

	Major lesions			
	Larger arteries		Smaller vessels	
Type of infarcts	Multiple territorial infarcts	Strategic territorial infarcts	Strategic lacunar infarcts	Multiple lacunar infarcts
Patho-genesis	cardial embolic art.emboli carot.stenosis	art.emboli embolic cardial	hyalinosis amyloidosis vasculitis thrombosis	Binswanger CADASIL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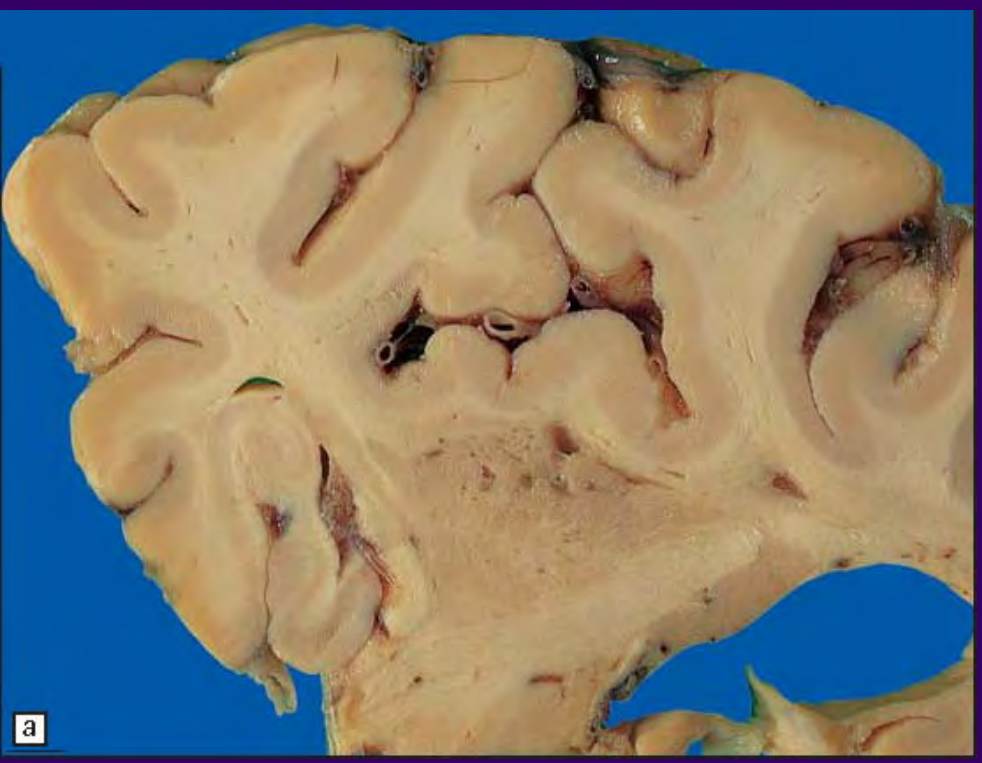
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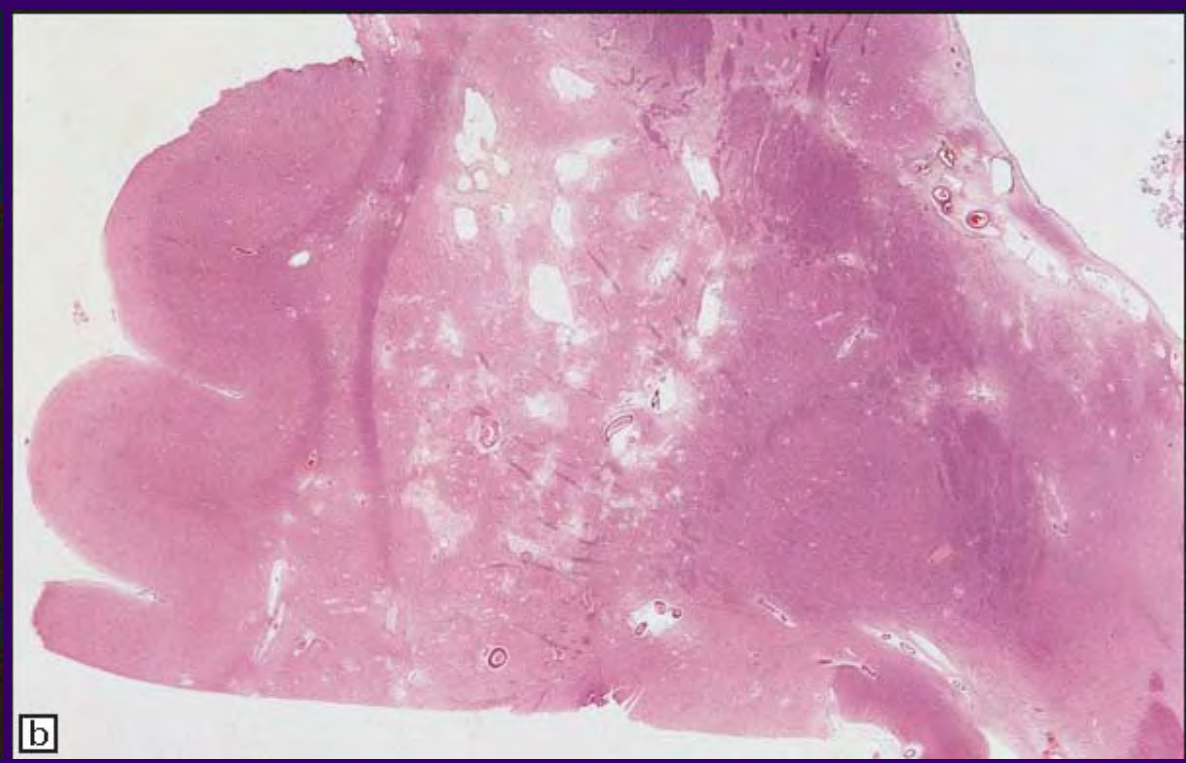
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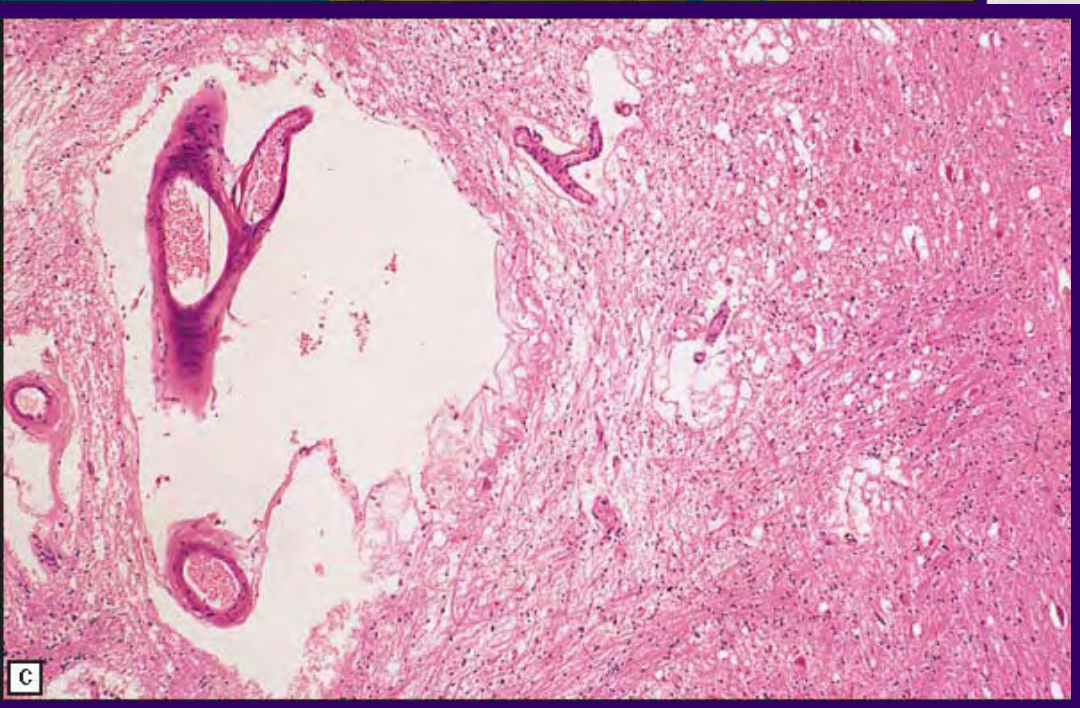
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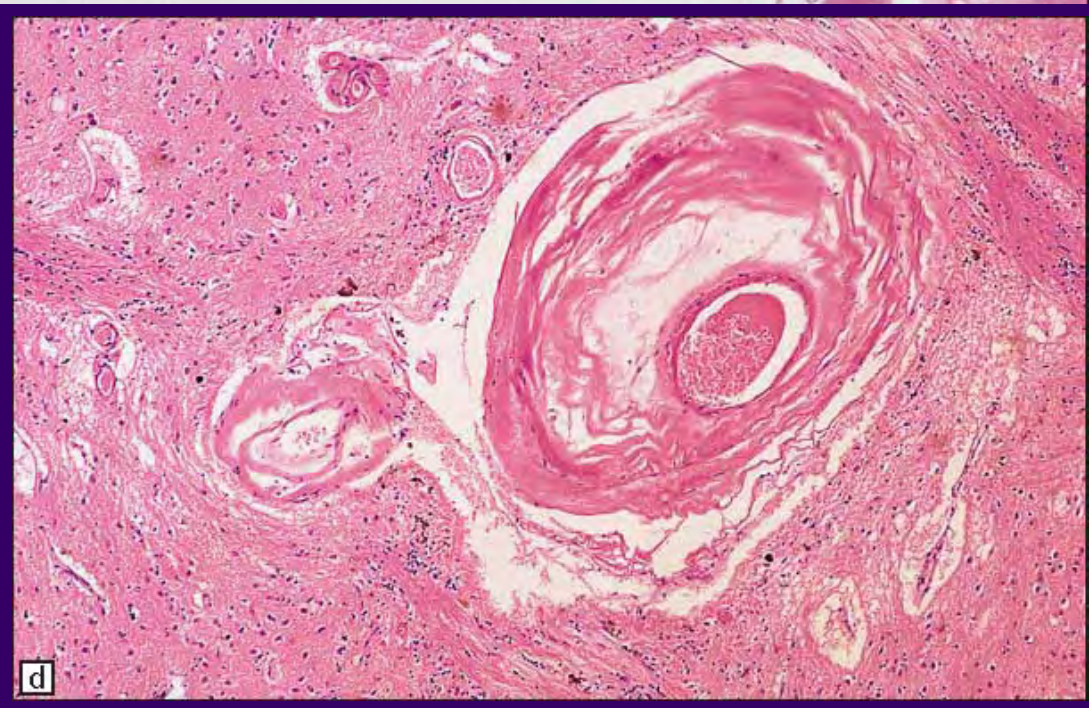
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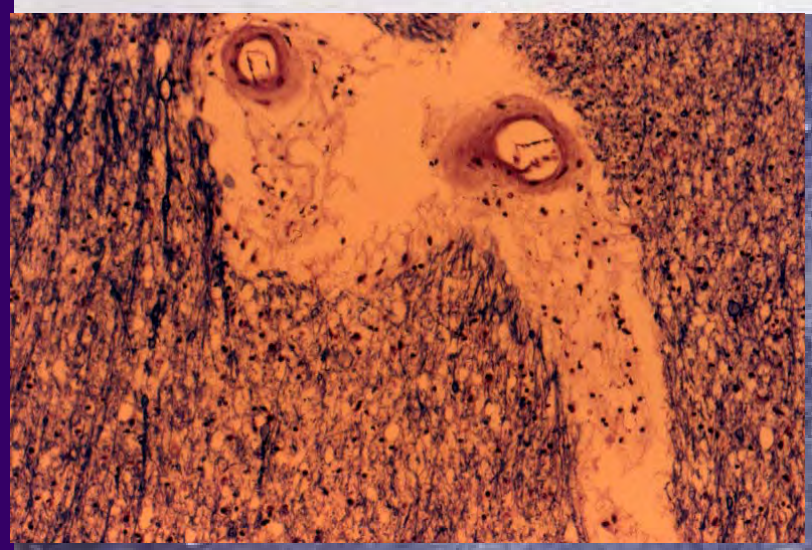
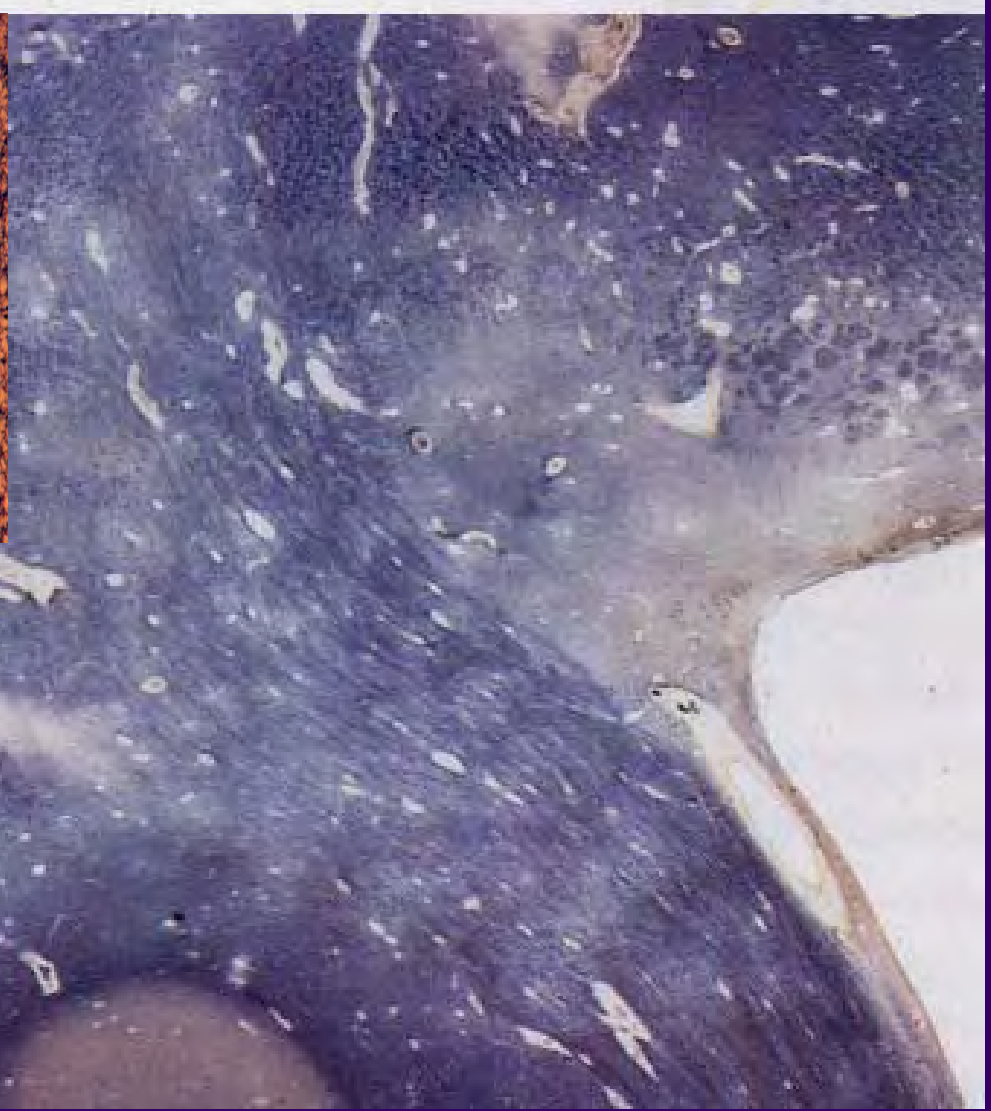
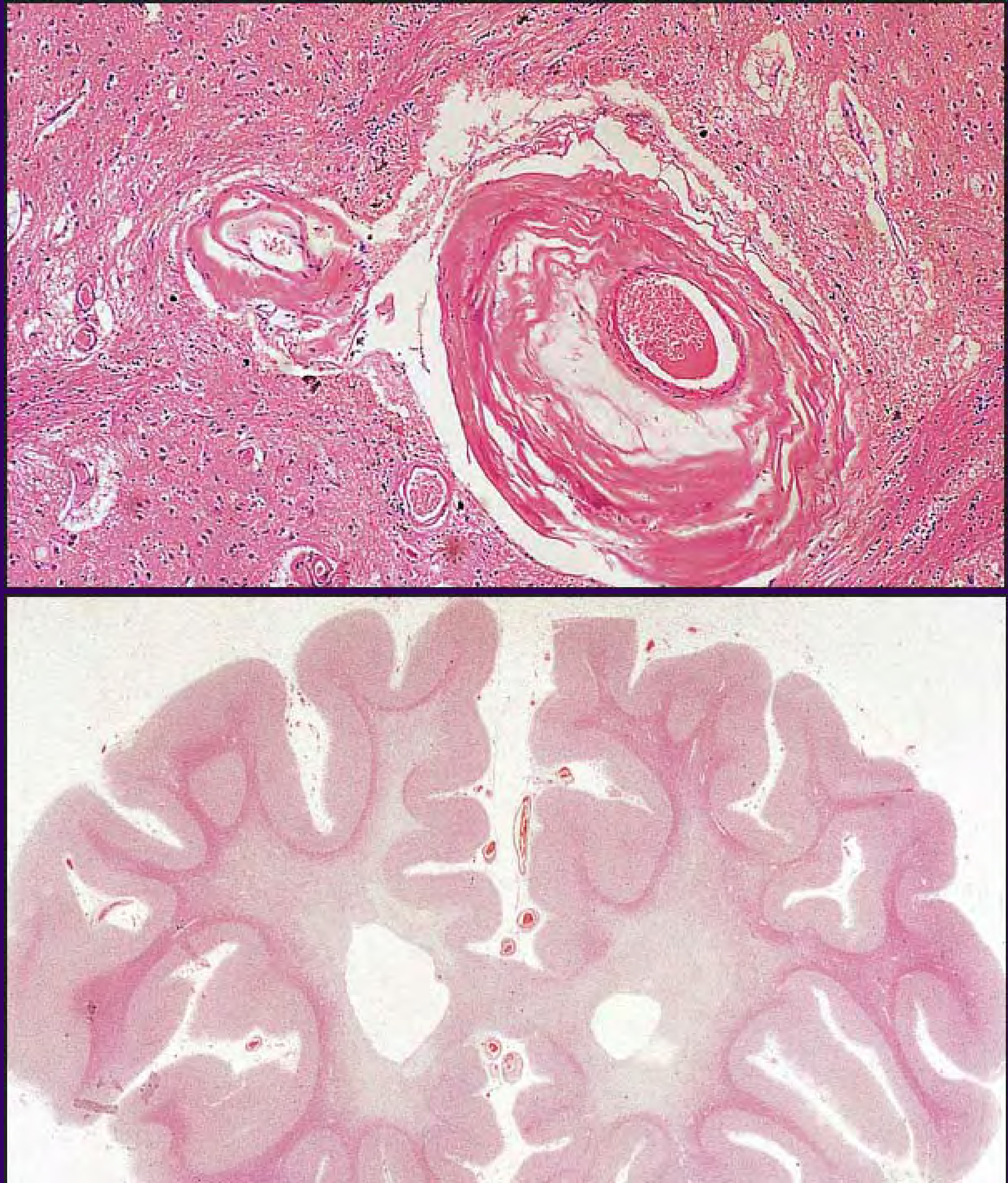
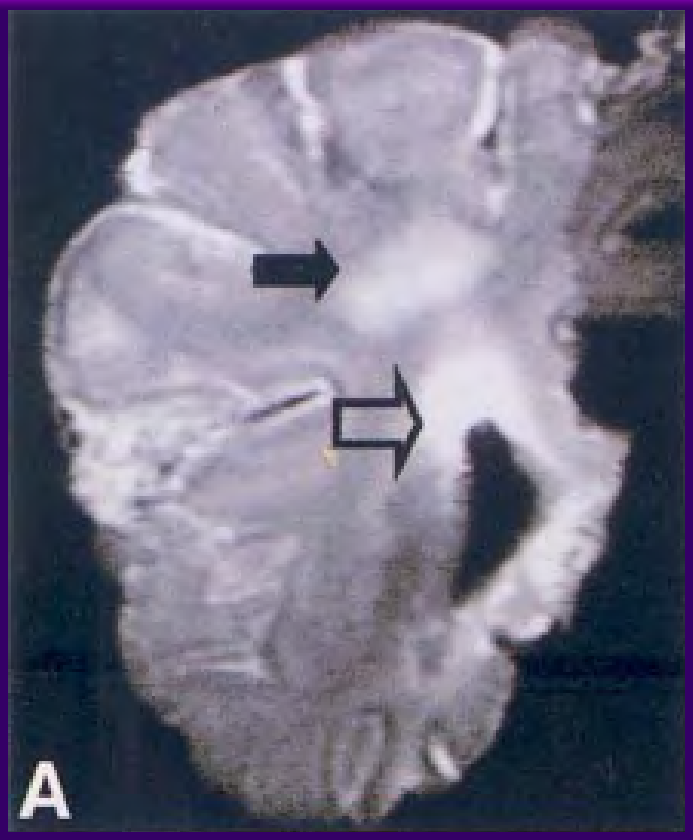


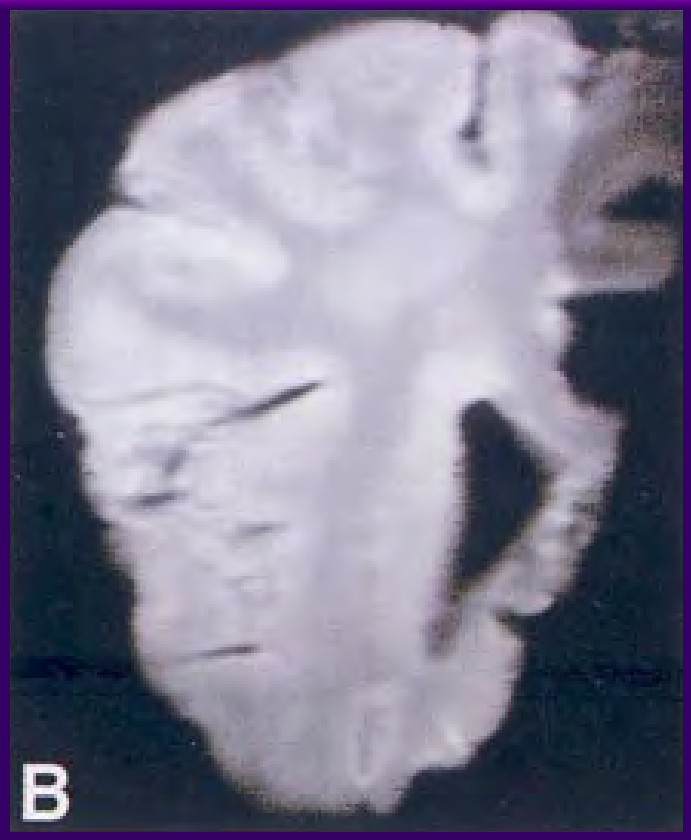


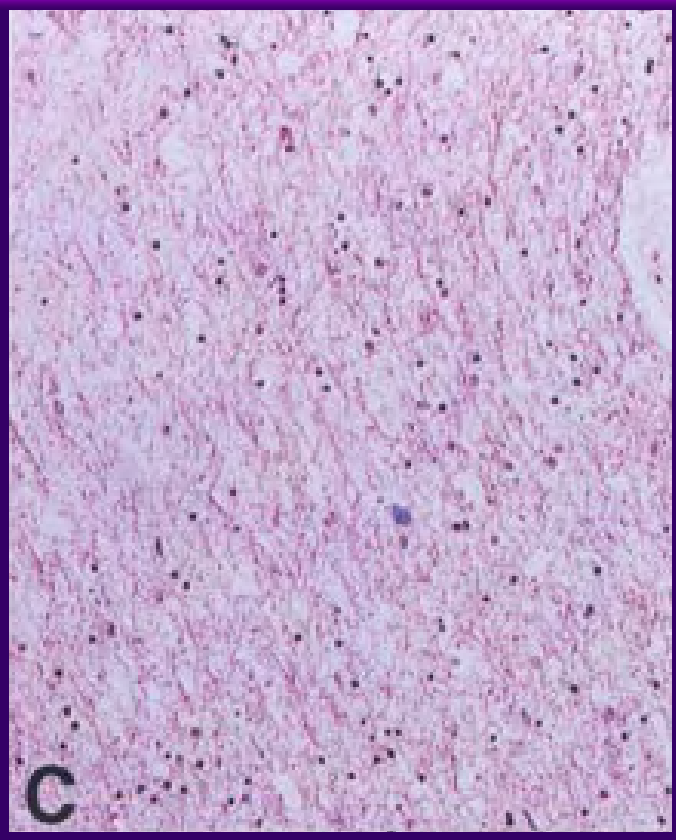


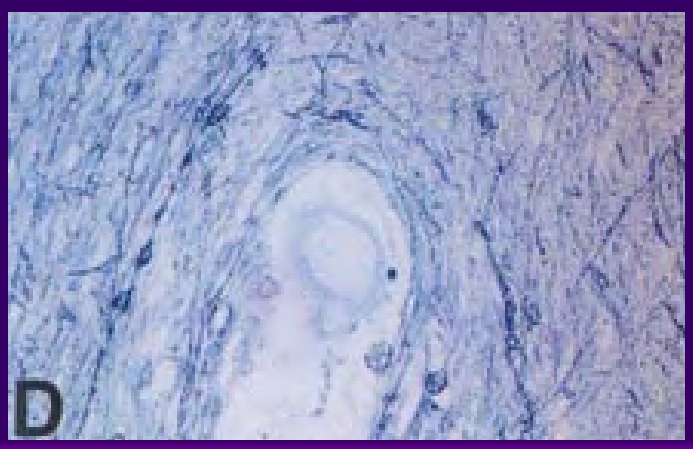
Periventricular white matter lesions.

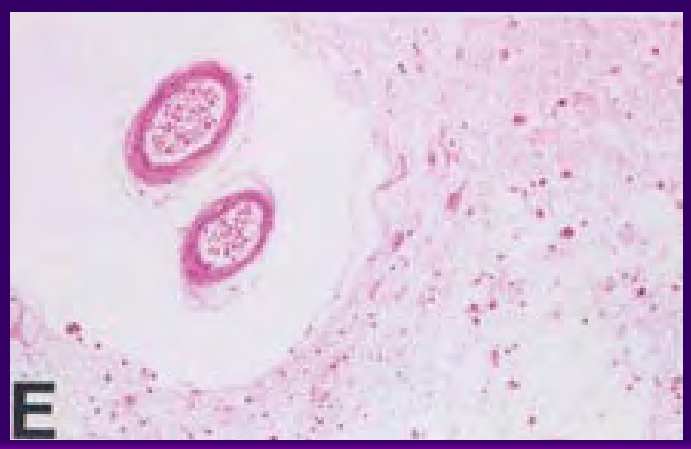
MRI and histology

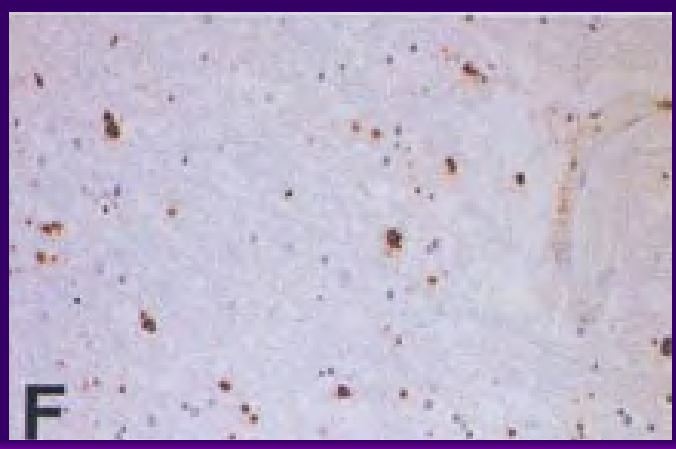




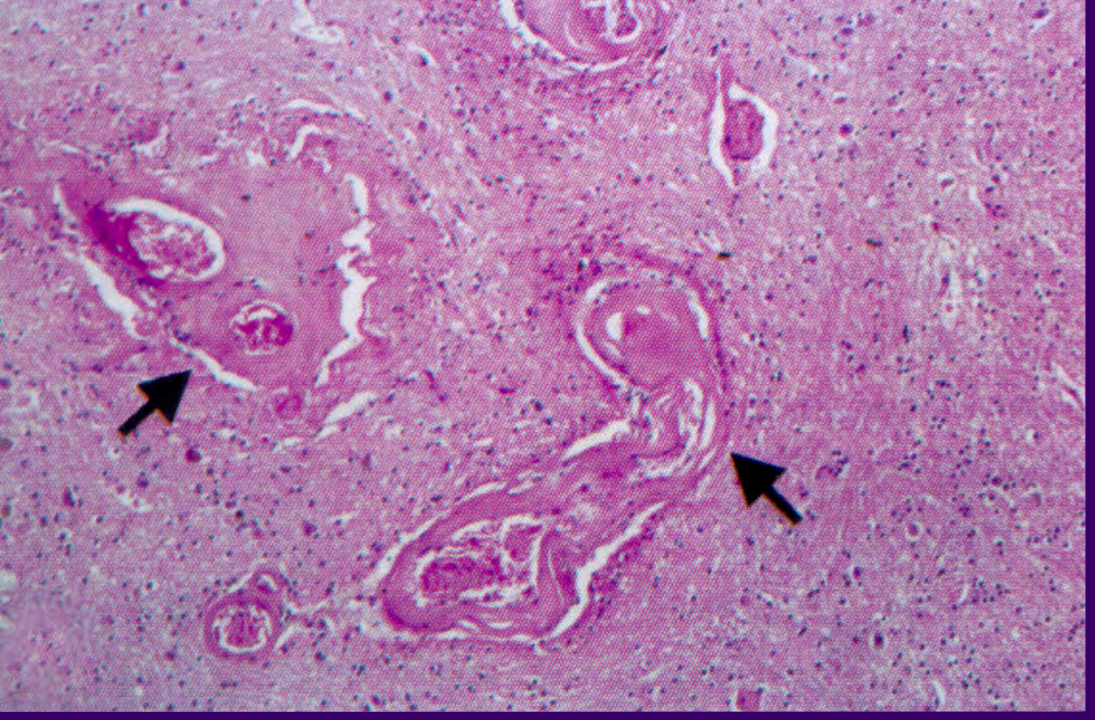


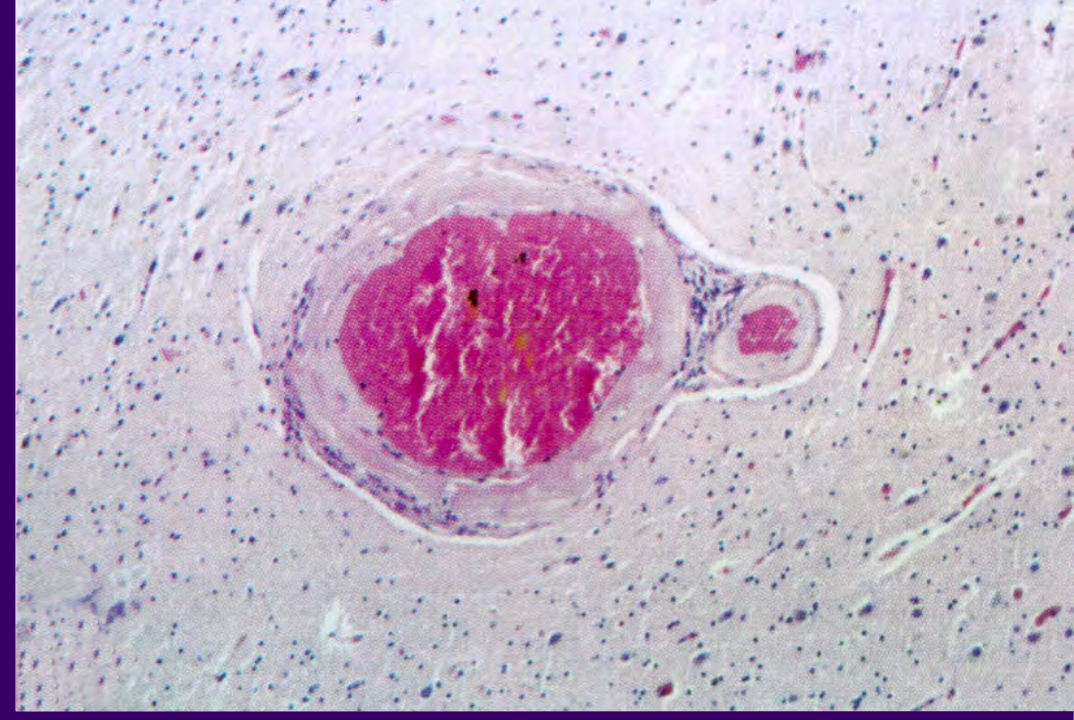


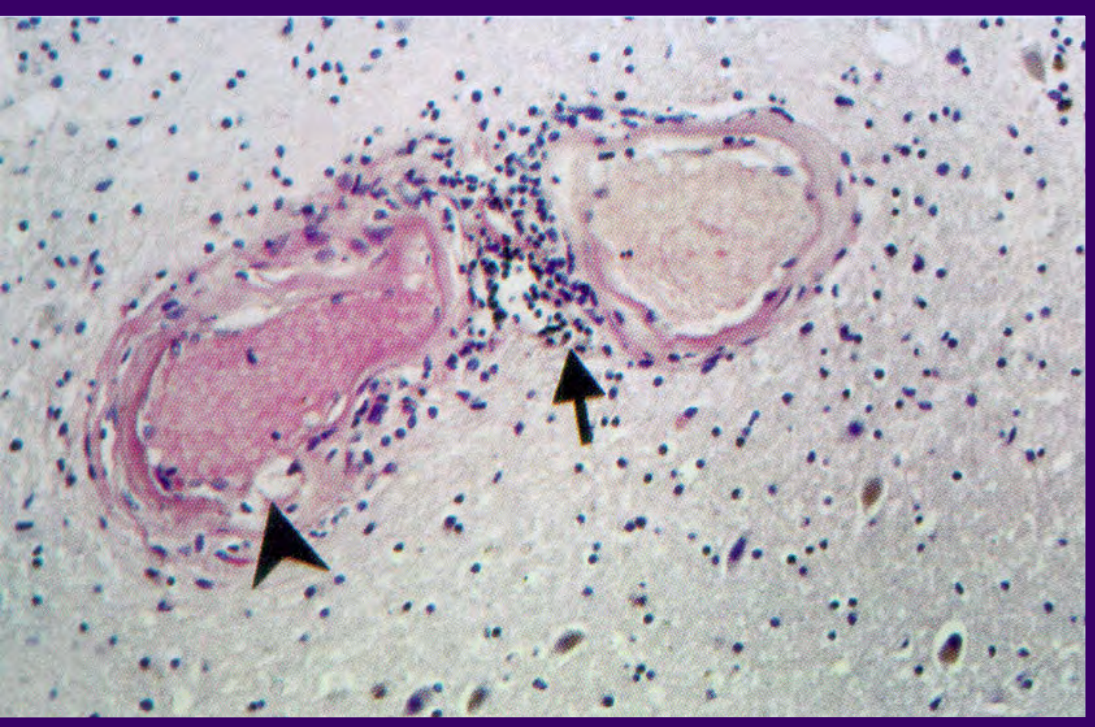


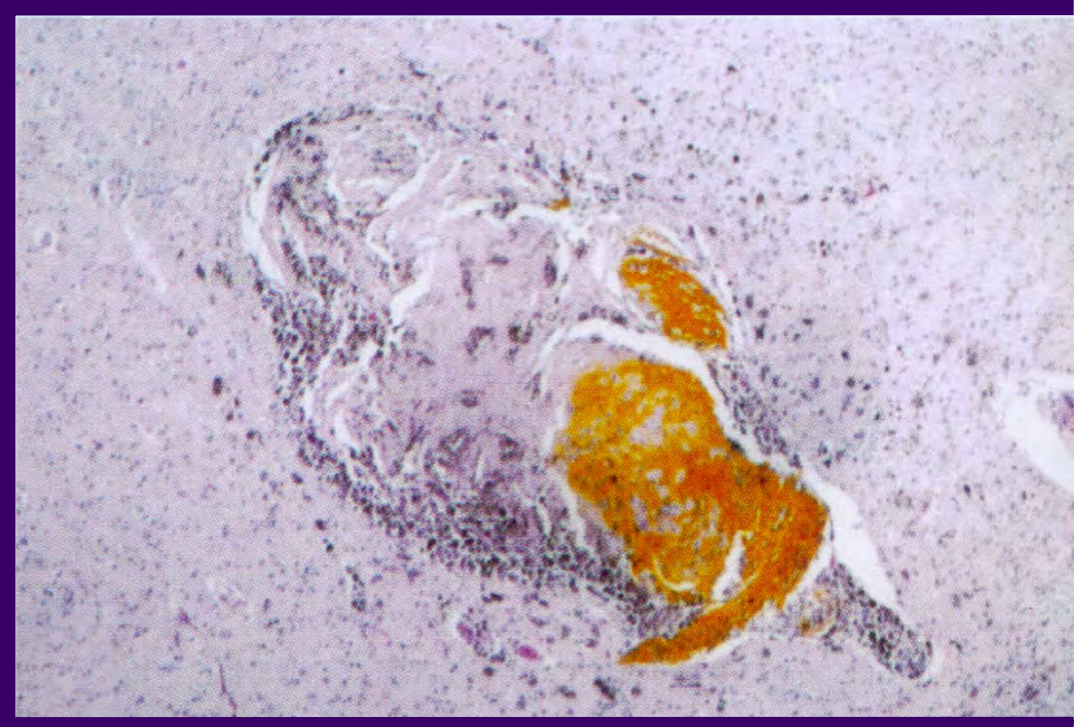


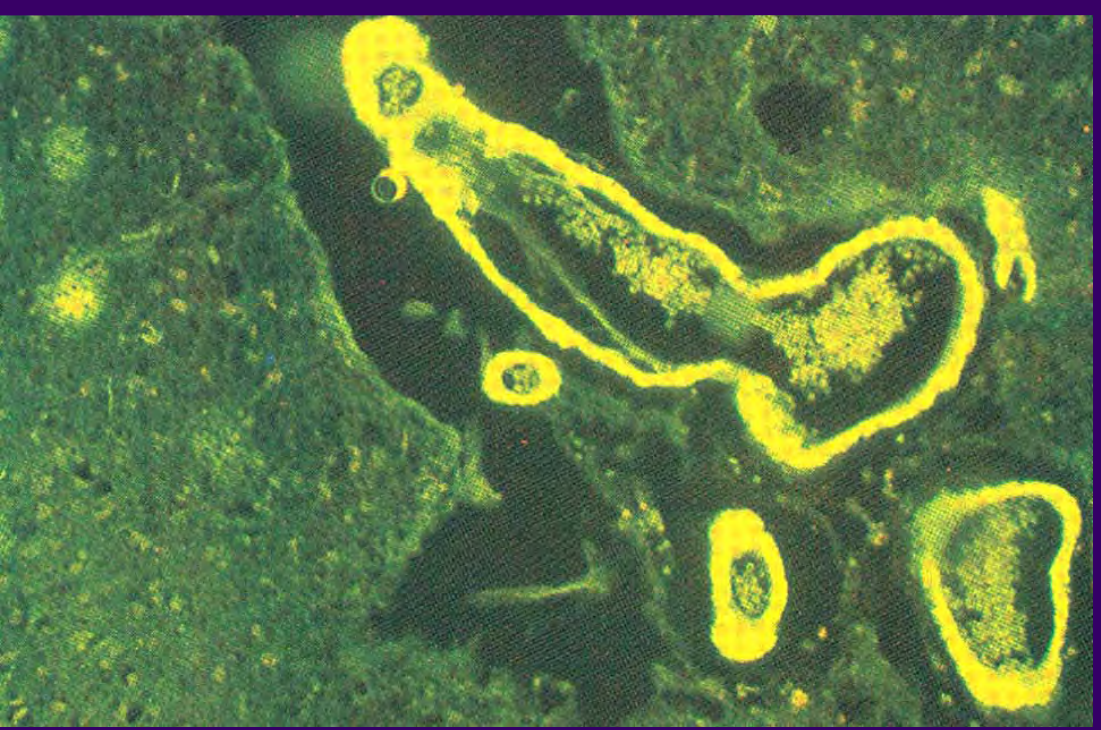
P.G. Ince, 2005

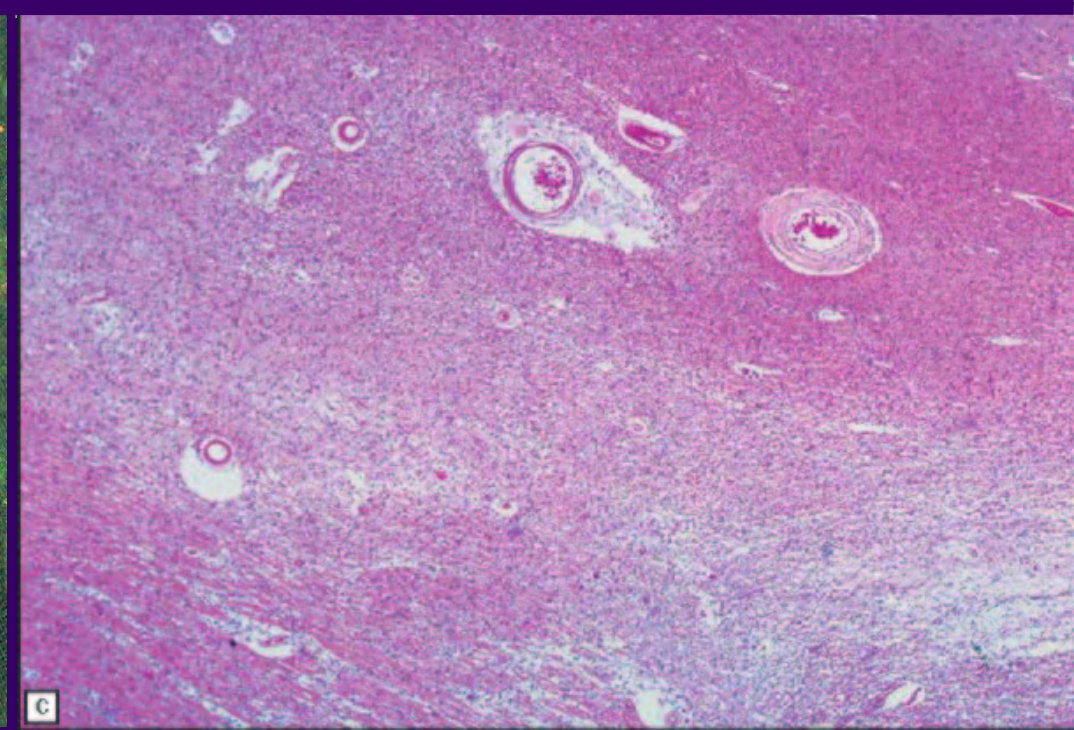








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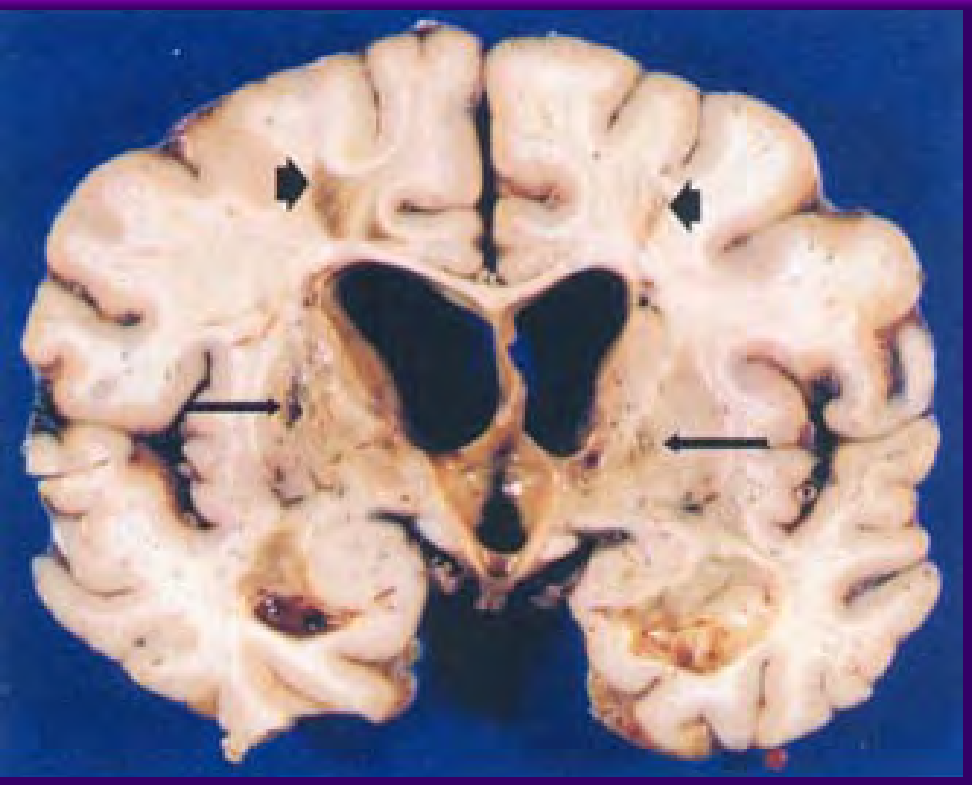
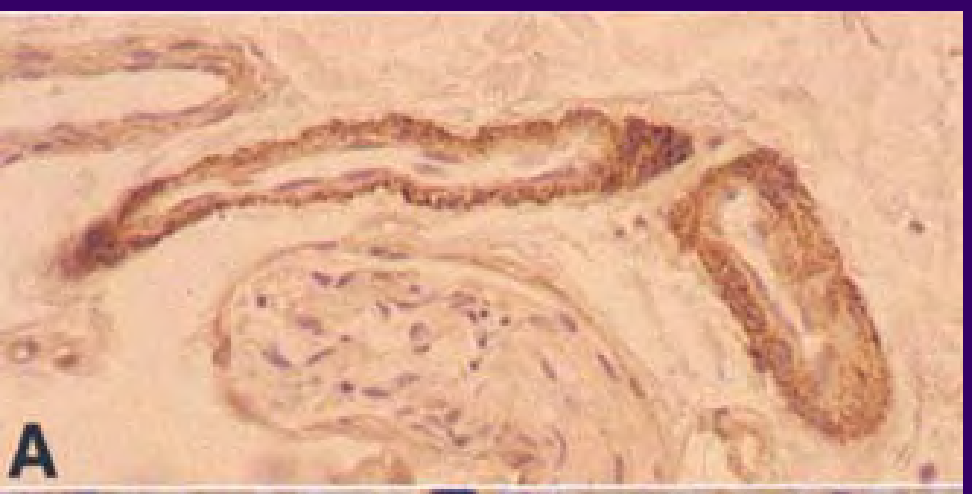
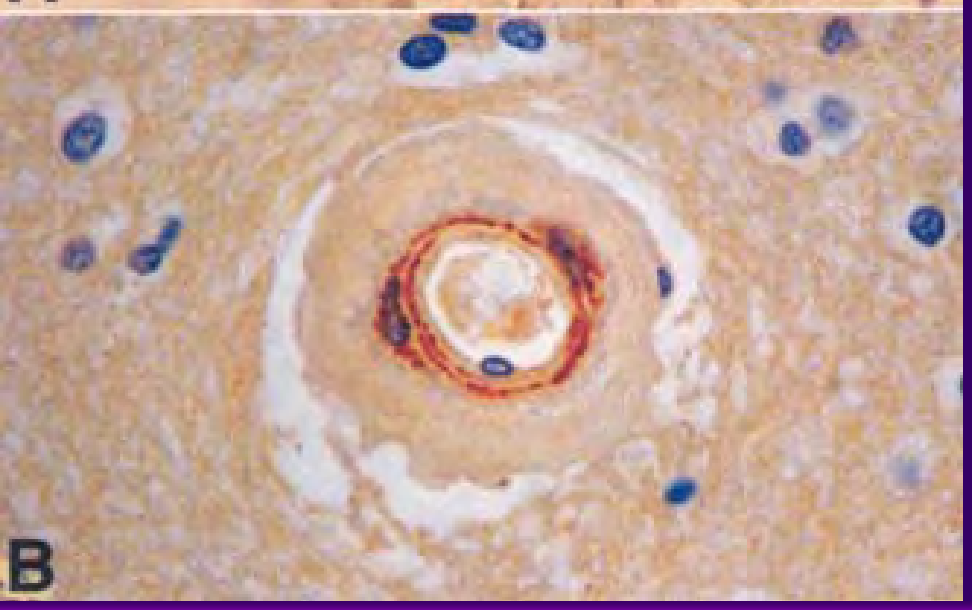
Strategic infarct syndrome

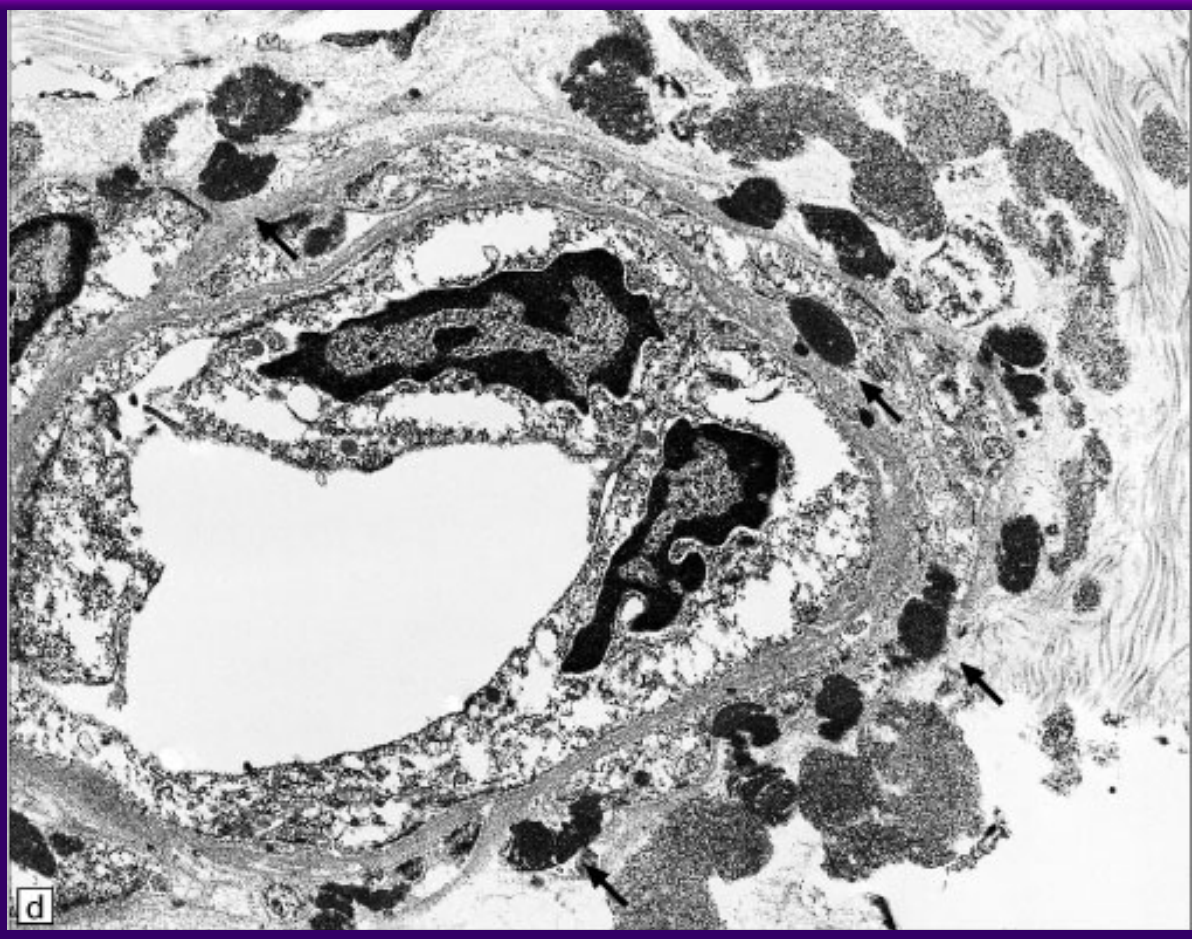
Vascular territory	Structures affected	Clinical features
anterior cerebral artery	medial frontal cortex	"frontal" behaviours (apathy, disinhibition. hyperorality, inappropriate sexuality, emotional lability); memory changes; hemiparesis
middle cerebral artery	angular gyrus	alexia; agraphia; fluent aphasia; memory changes; abnormal spatial awareness
middle cerebral artery boundary regions	cerebral convexity cortical "watersheds"	amnesia; apraxia; aphasia; agnosia; hemi-neglect; visual disturbances
posterior cerebral artery	hippocampus	amnesia; anomia, visual field disturbances; confusion
posterior cerebral artery	medial thalamic nuclei	memory impairment (especially memory acquisition); inattention

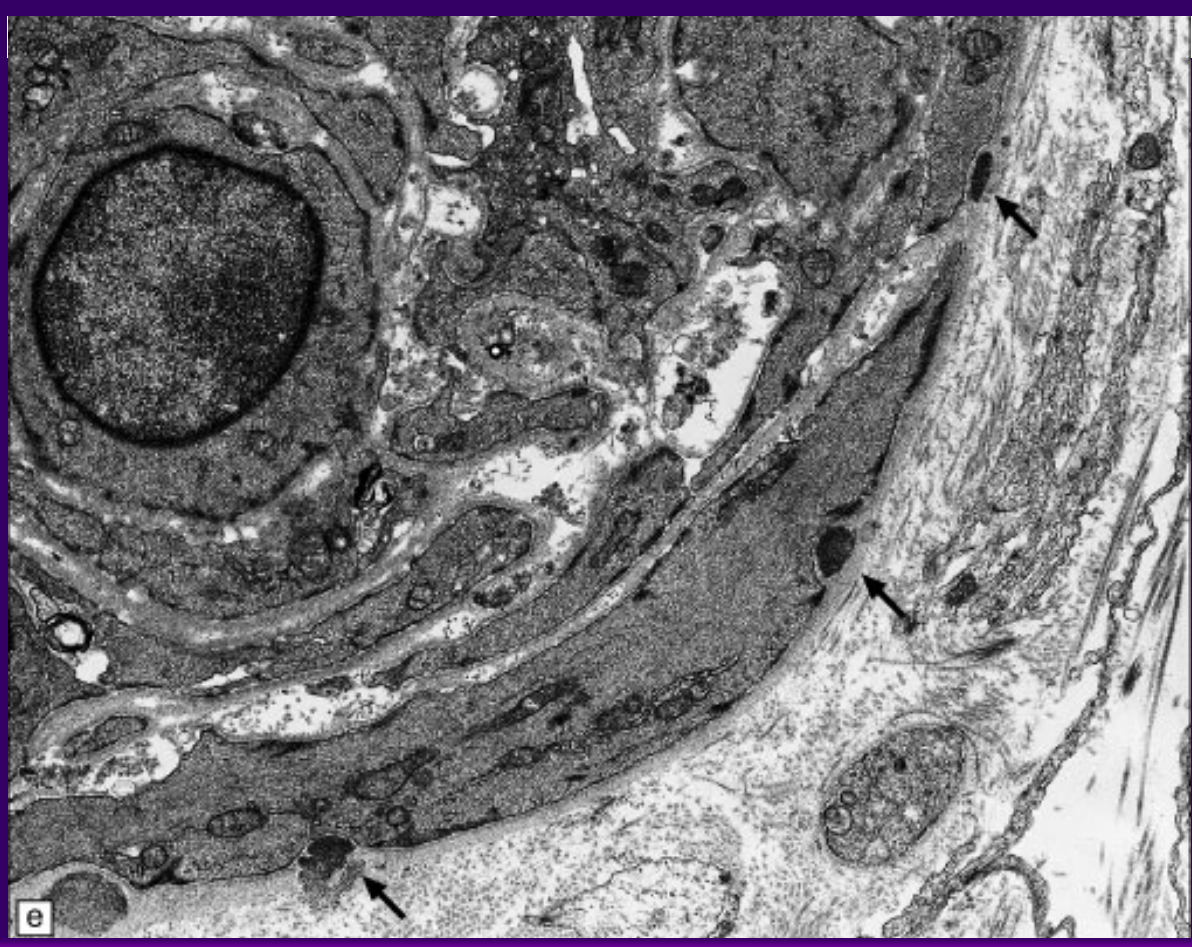
CADASIL











Kalimo & Kalaria, 2005

Ellison et al, 2004

Types of brain injury in vascular-ischemic encephalopathy

Category /MMSE (mean)	N pat (fem./male)	Braak stage Mean age	Cystic infarcts (mean age)	Lacunes (mean age)	Microinfarcts (mean age)	Hippocampal sclerosis
Dementia						
10±4	93 (54/39)	83.8	2.0	28 (81.6)	45 (82.3)[a]	17 (80.7)[b]	3 (84.0)[c]
Cognitively impaired						
(~22)	7 (5/2)	83.8	2.1	0	6[d]	1	0
Cognitively normal						
(~28)	5 (4/1)	77.8	1.2	1	4	0	0
Total	100 + 5			29	55	18	3

[a] two cases associated with hippocampal sclerosis, one with subcortical microinfarcts

[b] one combined with multiple subcortical lacunes, one with cystic infarcts in left PCA area

[c] eight combined with lacunes in striatum and thalamus

[d] one with incidental Lewy body disease

Autopsy series showing prevalence of VaD / VCI

(modified from Jellinger 2004)

1962-1990 15 studies (Europe, USA, Canada)
2784 cases
prevalence 2.0 - 85.2 % (mean 24.5 %)

1962-1995 *Markesberry (1998)*
prevalence mean 11.3 %

1991-2003 11 studies (USA, Scandinavia, Japan)
3438 cases
prevalence 0.03 - 35 % (mean 11.6 %)

2005 Austria, *Jellinger*: retrospective, dementia / AD
850 / 1500 cases
prevalence 10.8 / 2.2 %

Austria, *Jellinger (unpubl.)*: prospect. dementias
180 cases
prevalence 7.8 %

Pathogenesis of vascular cognitive impairment *I.*

Tissue Lesions	Multifocal	Focal
Circulation Disorders Causes: Systemic disease Atherosclerosis Thrombo-embolism Cardiac disease Systemic emboli	multiple infarcts lacunes borderline infarcts cort. granular atrophy combined cortical-subcortical lesions	strategic regions (thalamus, caudate, hippocampus, angular, cing.gyri)
Hypoperfusion (instable arter. pressure)	incomplete infarcts, white matter lesions (leukoaraiosis, Binswanger)	periventricular lesions
Hemorrhagic	multiple hemorrhages	focal bleeds

Pathogenesis of vascular cognitive impairment *II*: Vascular lesions

Atherosclerosis (large, small arteries)

Lipohyalinosis, fibrosis

Fibrinoid necrosis (hypertension)

Cer. amyloid angiopathy

CADASIL

Other hereditary angiopathies

Vasculitides (infectious, non-infectious)

System. microangiopathies (MELAS)

Thrombophlebitis, large sinuses

Art.-ven.malformations

Fibromuscular dysplasia (rare)

Intravasale lymphomatosis

Histopathology of Alzheimer's disease - diagnostic markers

β-amyloid (Aβ) deposition ⟷ **Cytoskeletal pathology**

Senile plaques

Amyloid angiopathy

Neurons:
Neurofibrillary tangles

Dendrites:
Neuropil threads

Neuropil:
Neuritic plaques

Paired helical filaments (PHF)

Loss of synapses / synaptic markers → Strategic spreading of cytoskeletal lesions

Allocortex (trans/entorhinal → hippocampus)
→ isocortex (association areas)
→ subcortical nuclei

Neuronal loss → cerebral atrophy

Microglial activation
(inflammatory? immunologic?)

Astroglial proliferation - Aβ synthesis/reactive

Diagnostic markers - semi-quantitative assessment
Neuritic plaques
Neurofibrillary tangles

Neuropathological criteria of Alzheimer disease

1. **Criteria according to Khachaturian (1985)**

   Senile (SP) or neuritic plaques (NP) in the presence of n eurofibrillary degeneration (NFT) in **neocortex** (any region)

   a) age < 50 a: 2 - 5/mm2
   b) age 50-60 a: ≥ 8/mm2
   c) age 66-75 a: > 10/mm2
   d) age > 75 a: > 15/mm2

2. **CERAD criteria (Mirra et al., 1993)**

   a) *definite* AD: "C" age-adapted plaque score * + clinical dementia
   b) *probable* AD: "B" age-adapted plaque score + clinical dementia presence / absence of other lesions causing or related to dementia

*** Age-adapted plaque score :**

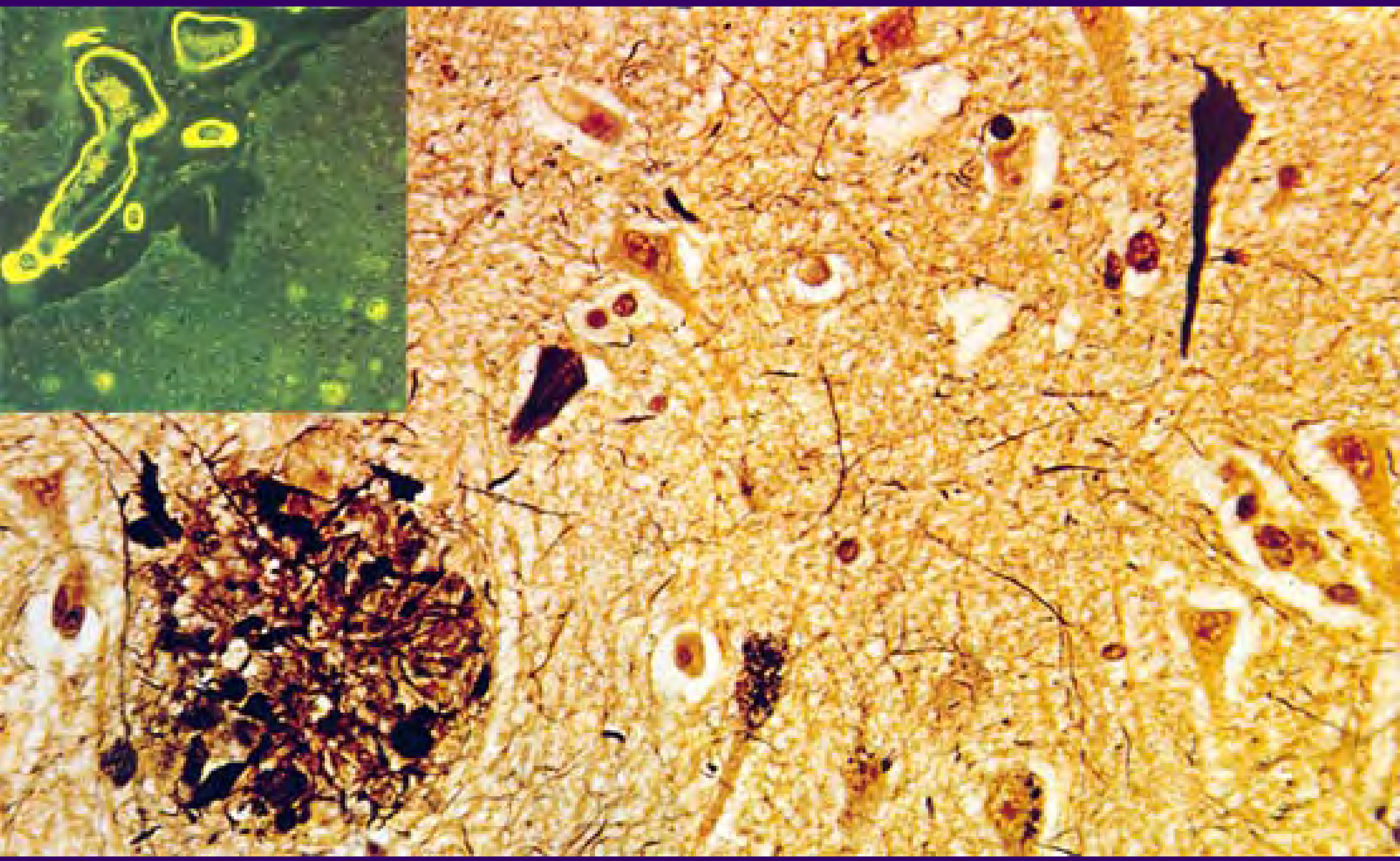
	Frequency of plaques			
Age at death	**none**	**few**	**moderate**	**numerous**
< 50 a	0	C	C	C
50 - 75	0	B	C	C
> 75	0	A	B	C

A = uncertain; B = probable; C = definite

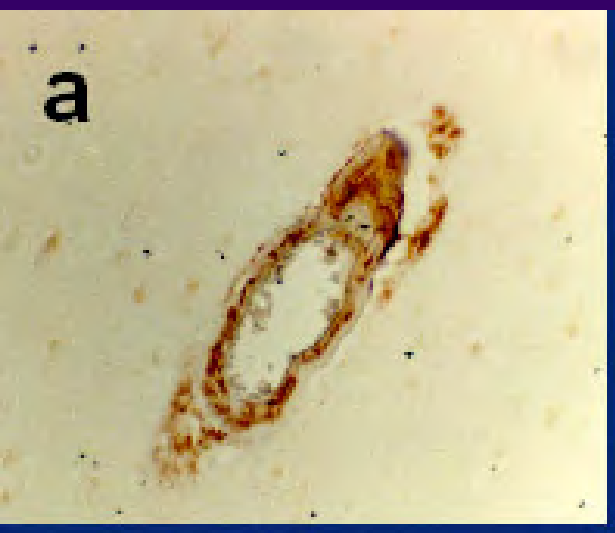
3. **NIA-Reagan Institute criteria (1997)**

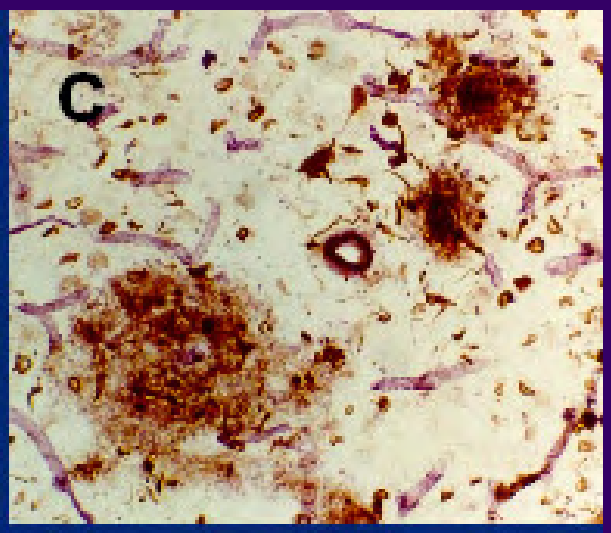
   probability statements based upon topographic "staging" of NFT and SP (CERAD score + Braak stages). *Probability* that dementia is caused by AD :

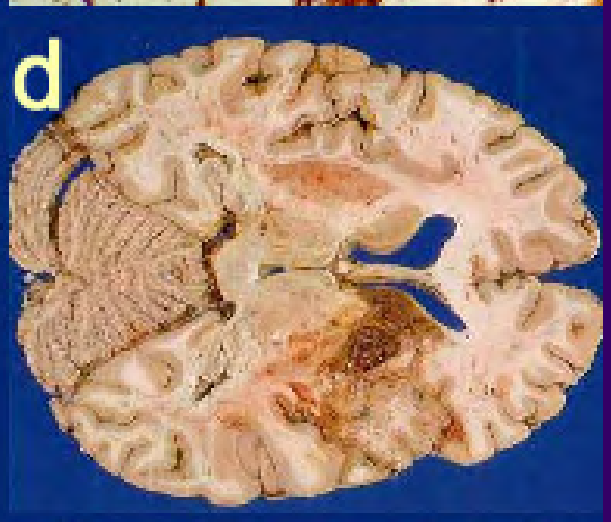
   low: CERAD 0-A, Braak 1-2
   intermediate: CERAD B, Braak 3-4
   high: CERAD B-C, Braak 5-6

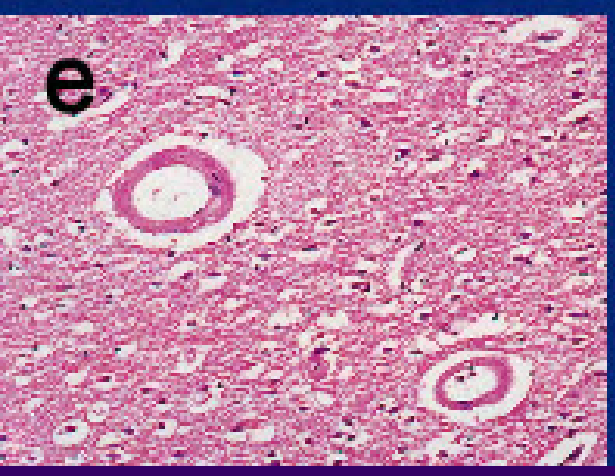


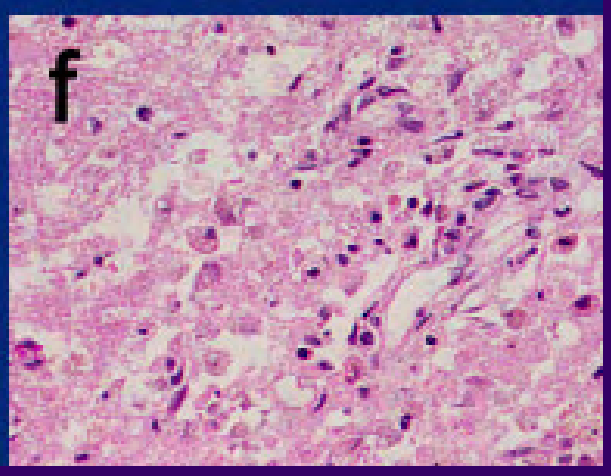
Vascular pathology in AD











a) Cerebral amyloid angiopathy

b) Microvascular degeneration/ arteriosclerosis

c) BBB leakage /serum proteins

d) Petechial / macrohaemorrhages

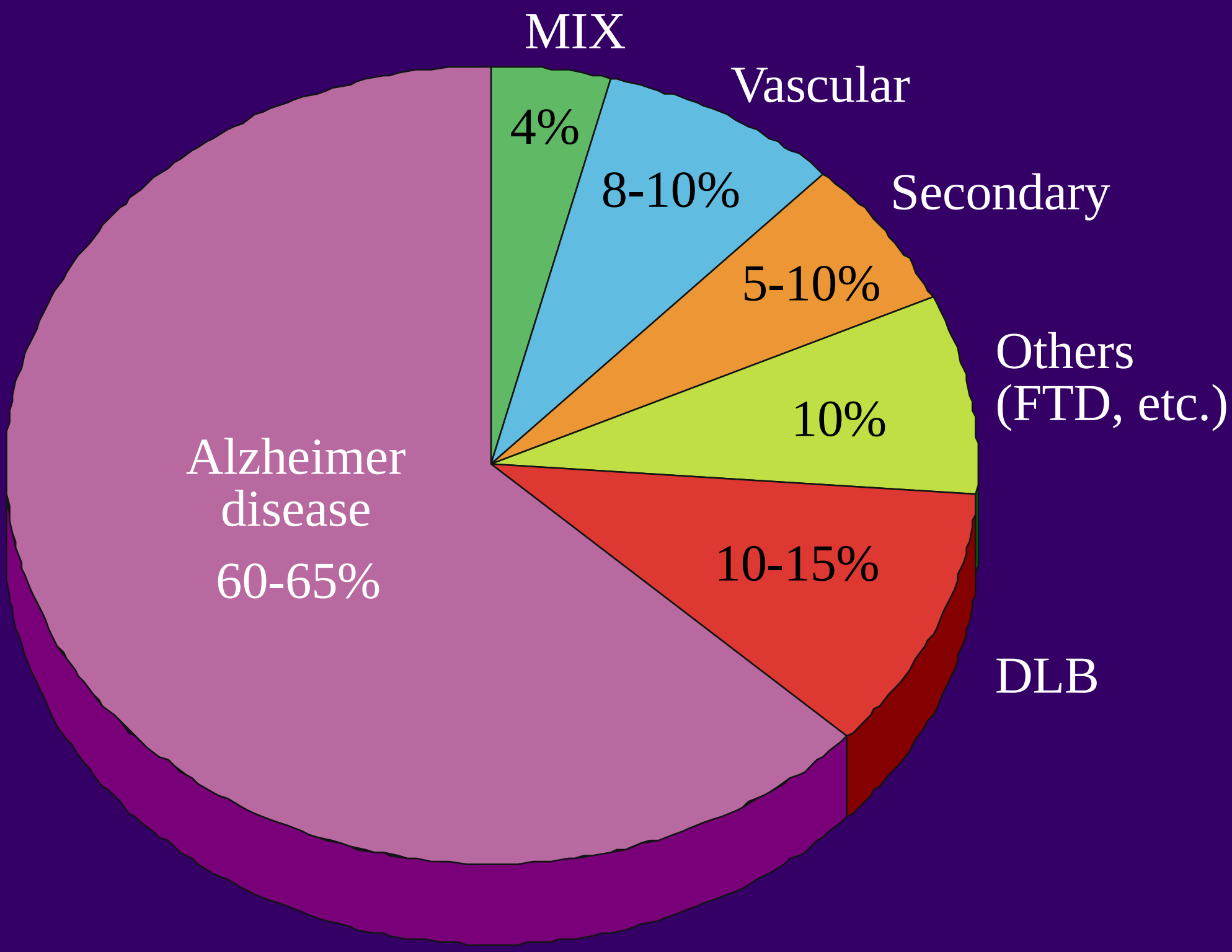
e, f) Large and micro-infarcts

- White matter lesions and lacunes

Prevalence of mixed dementia (AD + VaD) in autopsy studies

Study	N	Mixed cases	%
Tomlinson et al (1970)	50	9	18.0
Todorov et al (1975)	776	250	32.0
Mölsä et al (1985)	58	6	10.3
Ulrich et al (1986)	54	6	11.0
Alafuzoff et al (1987)	55	15	27.0
Joachim et al (1988)	150	10	7.0
Katzman et al (1988)	3 series	(<70 years) (>70 years)	0.6 15.2
Boller et al (1989)	54	2	3.7
O'Brien (1988)	?	?	10.0
Jellinger et al (1990)	675	53	7.9
Brun (1994)	175	63	36.0
Ince et al (1995)	69	4	5.9
Markesbery (1998)	mixed series		mean 17.7
Knopman et al (2003)	81	10	12.2
Jellinger & Attems (2006) (dementias/clinical AD)	1500/850	68/21	4.6/2.4
Jellinger (unpubl.) prospective study	180	8	4.4

Incidence of frequent forms of dementia



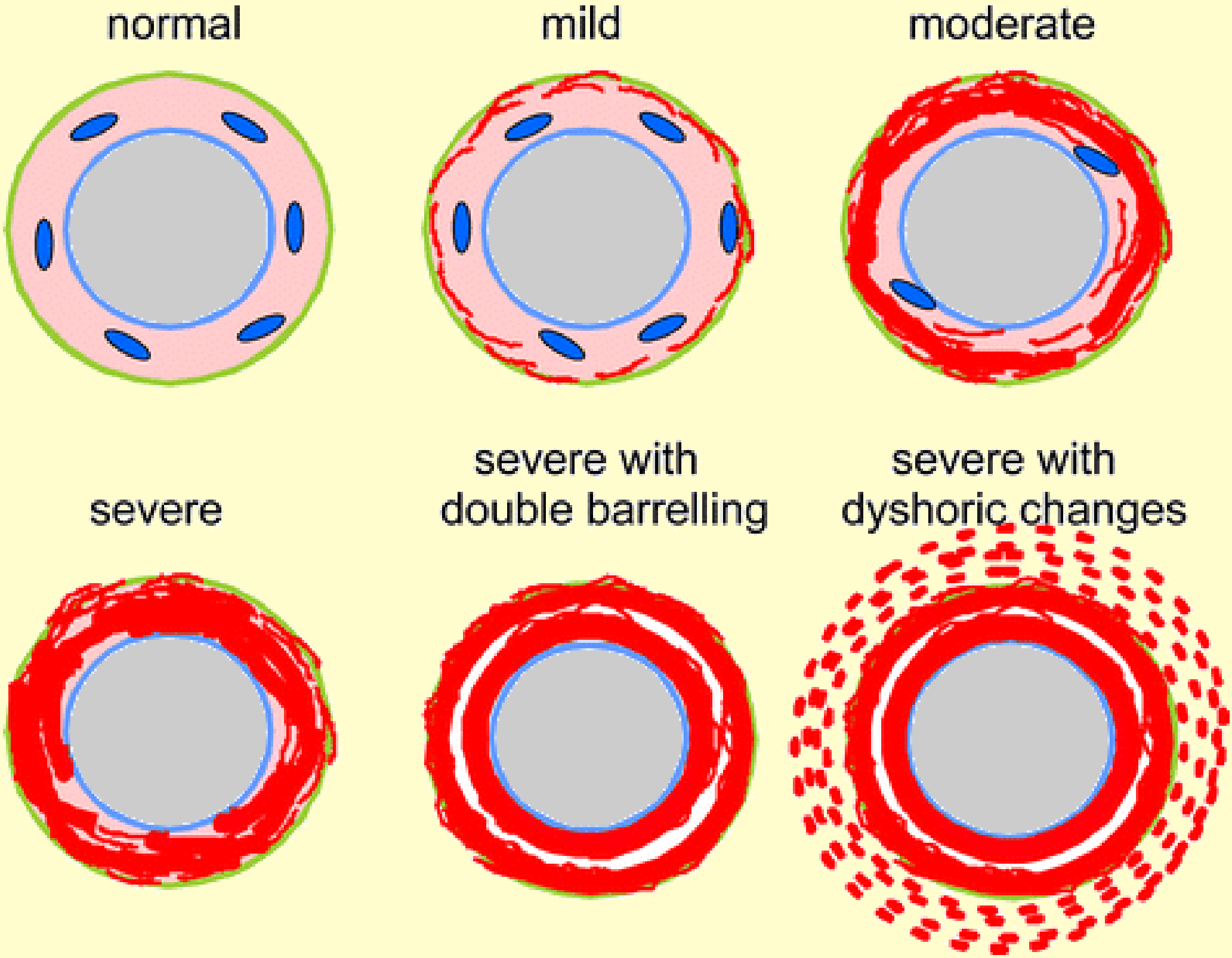
Morphologic diagnosis in consecutive Vienna autopsy series of demented aged persons (A) and AD (B) (1989-2005)

Morphological diagnosis	(A) n	(A) %	(B) n	(B) %
"Pure" AD (CERAD pos., Braak V-VI)	600	40.0	431	50.7
Alzheimer type path, (plaque, limbic, NFT/SD) (28/48/30, 11/19/19)	106	7.1	49	5.8
AD + CVD (lacunar state, old/acute infarcts old, AH-sclerosis (147/57/36/18, 120/47/13/13)	258	17.2	193	22.7
AD + cerebral hemorrhage (CAA)	44	2.9	17	2.0
Lewy body variant AD / Diff. LB dis. (38/27, 25/7)	65	4.3	32	3.8
AD + Parkinson pathol., PD, Incid, LBD, SN lesions (45/18/8, 21/12/8)	71	4.7	41	4.8
MIX type dem, (AD+MIE, +SAE, +SID) (39/22/7, 13/7/1)	68	4.5	21	2.4
AD + other pathol. (tumors, MS, MSA, etc.)	38	2.5	10	1.2
Alzheimer pathology total	*1250*	*83.3*	*794*	*93.4*
Vasc. dem. (MIE, SAE, SID, Ath.scler.) (54/80/25/3, 7/7/8)	162	10.8	22	2.6
Other disorders (Huntington dis., FTD, CJD, etc)	73	4.5	28	3.3
Nothing abnormal beyond age	15	1.0	6	0.7
Non-Alzheimer pathologies	*250*	*16.7*	*56*	*6.6*
Total	*1500*	*100.0*	*850*	*100.0*

Mixed pathologies frequent in demented elderly

Author	n	Pathologies [%]				
		AD lesions	AD alone	AD+ CVL	AD+ DLB	VaD
Nolan et al '98	87	87	50	34	–	–
Lim et al '99	?	AD cases	36	45	22	–
NUN study Riley et al '02		AD cases	57	73/93	–	–
HAAS study Petrovich '05	333	< 60	36	24	–	24
MRC-CFAS (UK) (Fernando-Ince '05)	209 (48% demented)	70	21	–	–	78
Andin et al '05	175 (clin. VaD)	–	72	–	28	
Jellinger '06 (retrospect.)	1500	83.7	40.6	20.0	12.0	10.8
Jellinger (prospective, unpubl.)	180	82.7	48.8	23.9	10.0	7.8

Progression of CAA



Prevalence of CAA

Controls

33 % total CAA: 11% mild-moderate CAA
22% severe CAA

AD

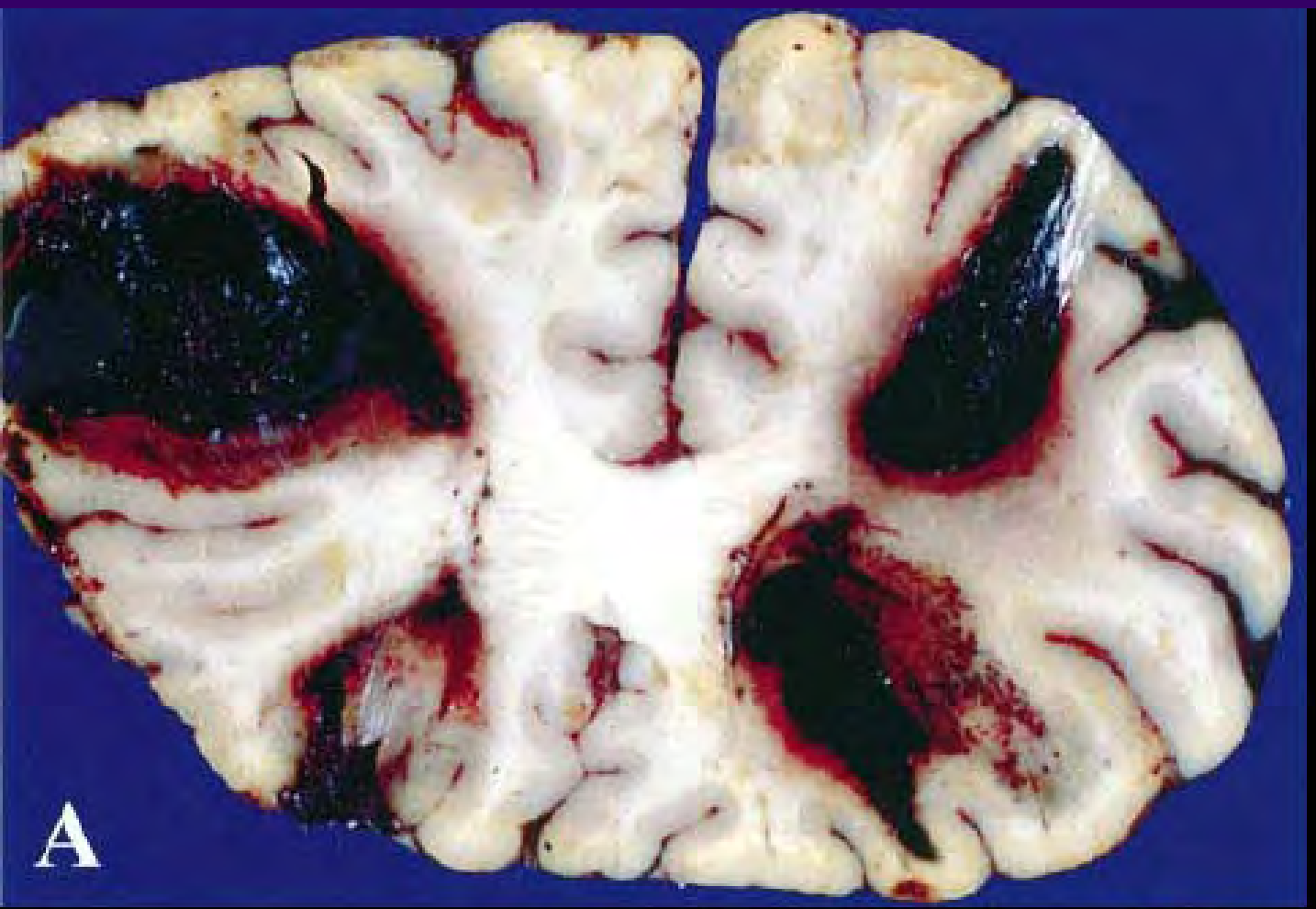
94-97.7 % total CAA (44% severe CAA)
Acute hemorrhages: 100 % severe CAA
Acute/old infarcts: 30 % severe CAA
70 % mild to moderate CAA

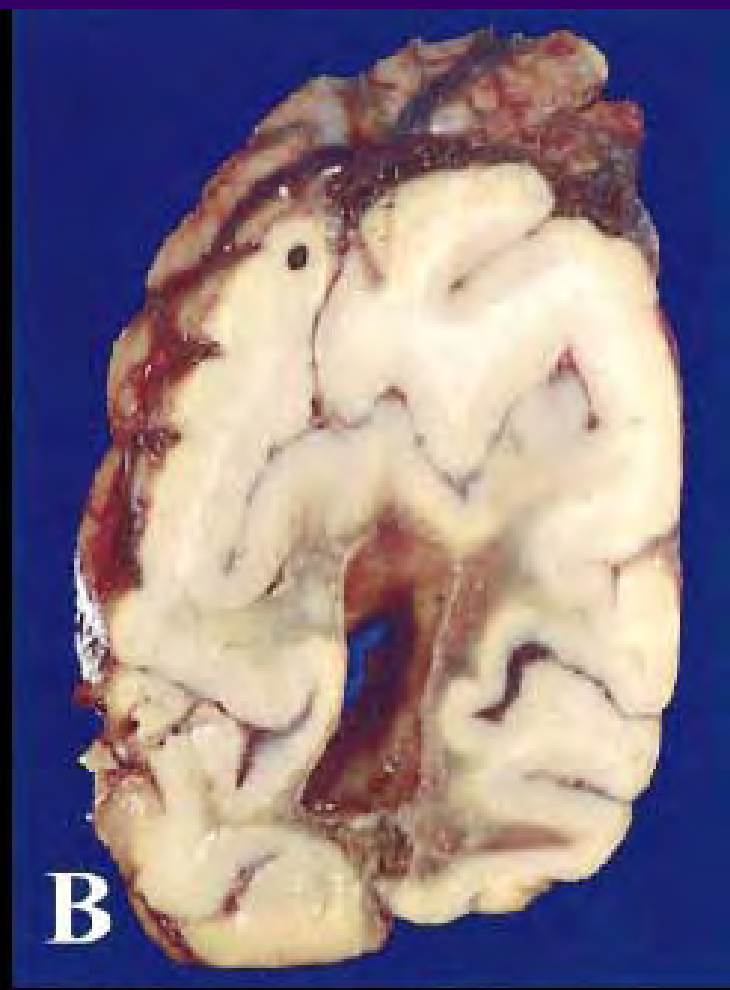
DLB

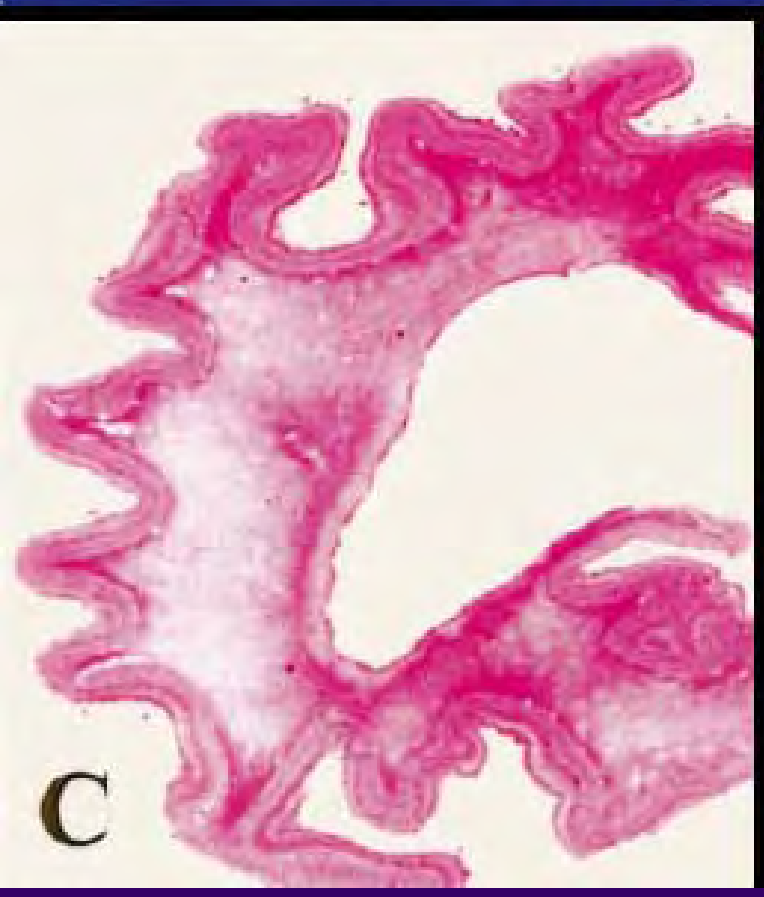
~ 45 % total CAA
24 % severe CAA (50 % with additional CVLs)

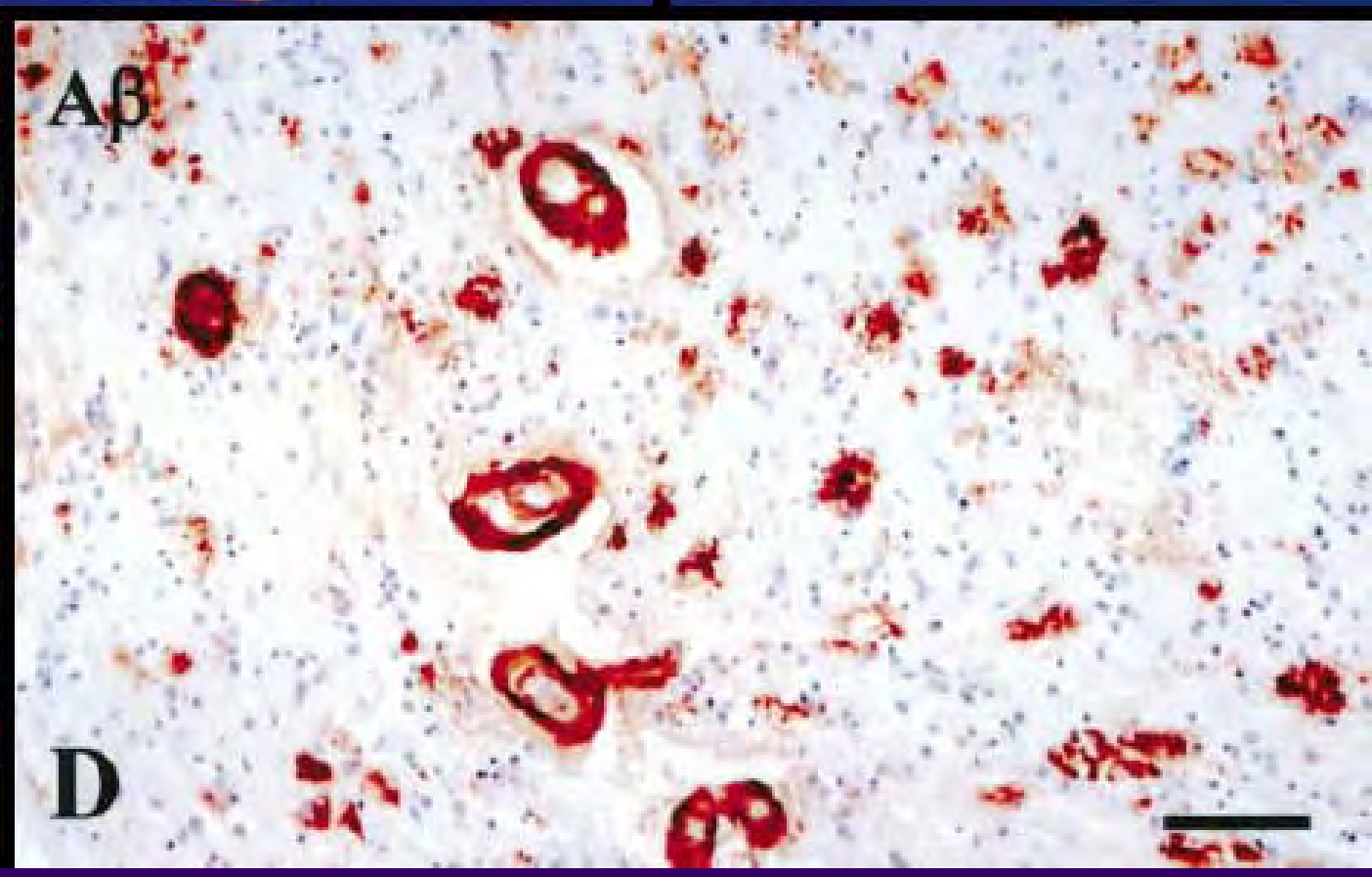
DDLB

27.7 % moderate-severe CAA
LBV/AD: 78 % total CAA
55 % severe CAA



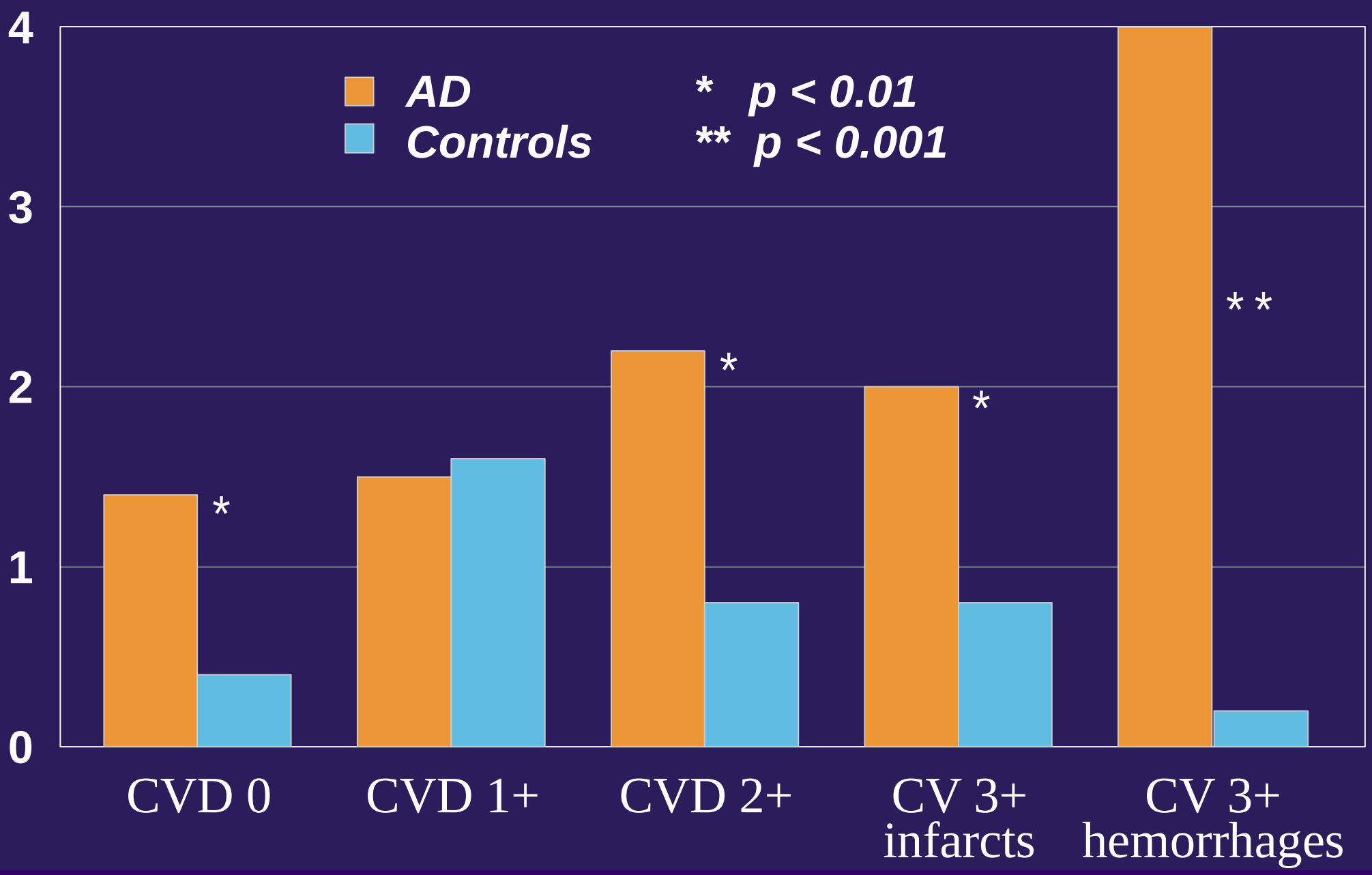






Revesz et al, JNEN 62, 2003

Severity of CAA in different types of cerebrovascular lesions in AD and controls

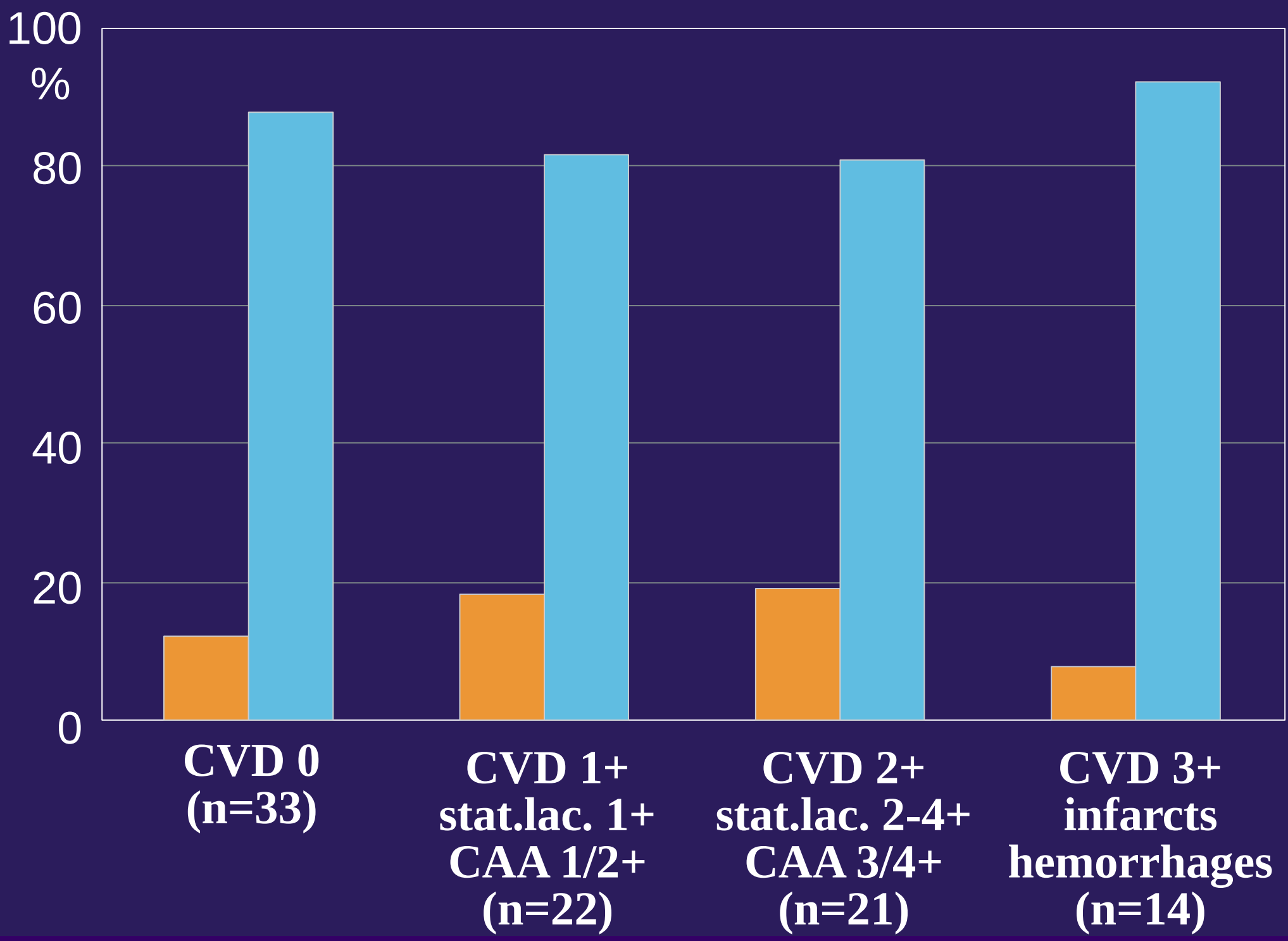


Relation between Braak stages and CVLs in AD brains

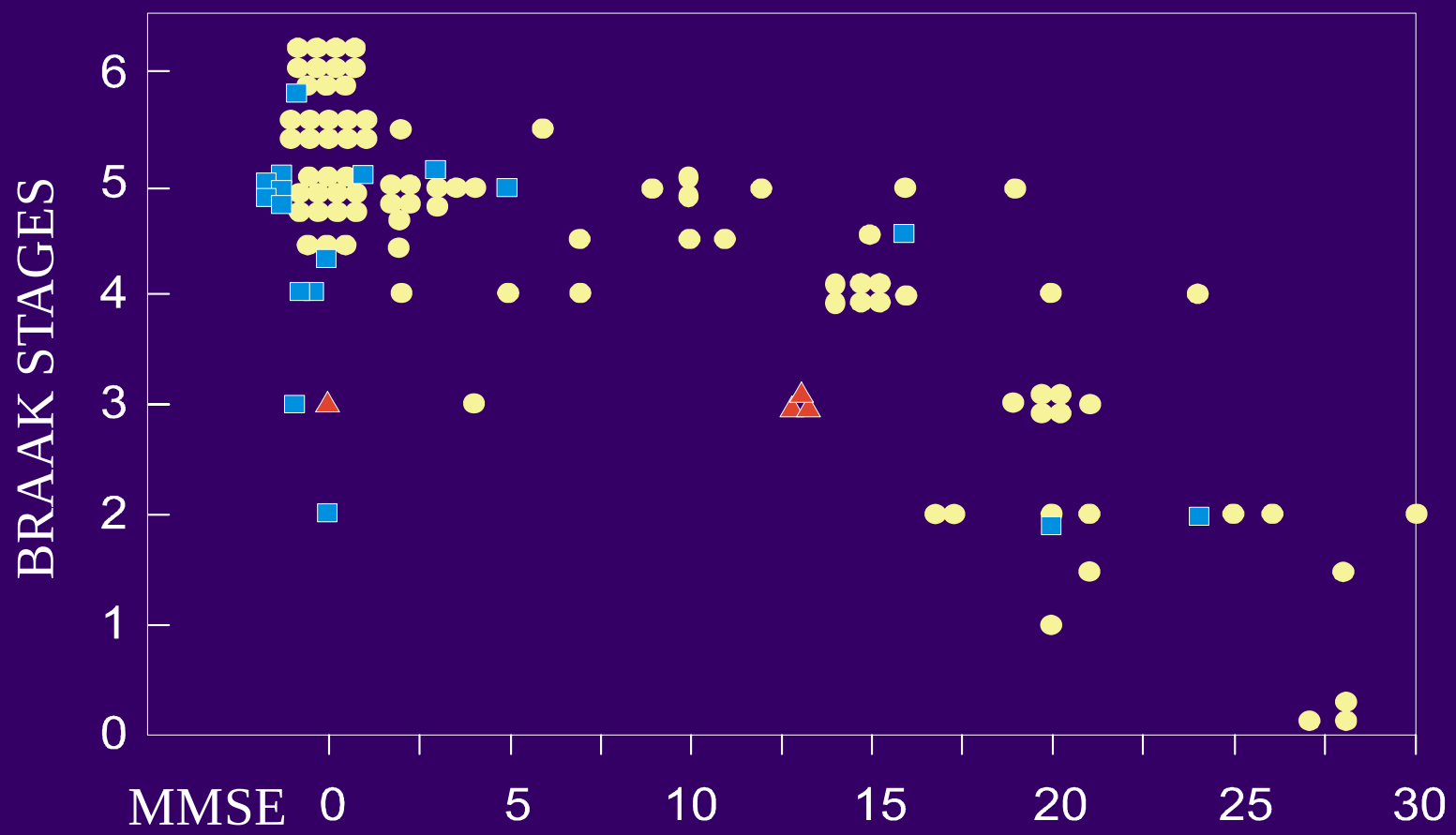
B / B4

B / B5/6

n = 90 (38 M, 52 F), age 62-103 (81±6.8)
MMSE = 0-17 (mean 3.1)
Apo Eε4 allele frequency = 28 %



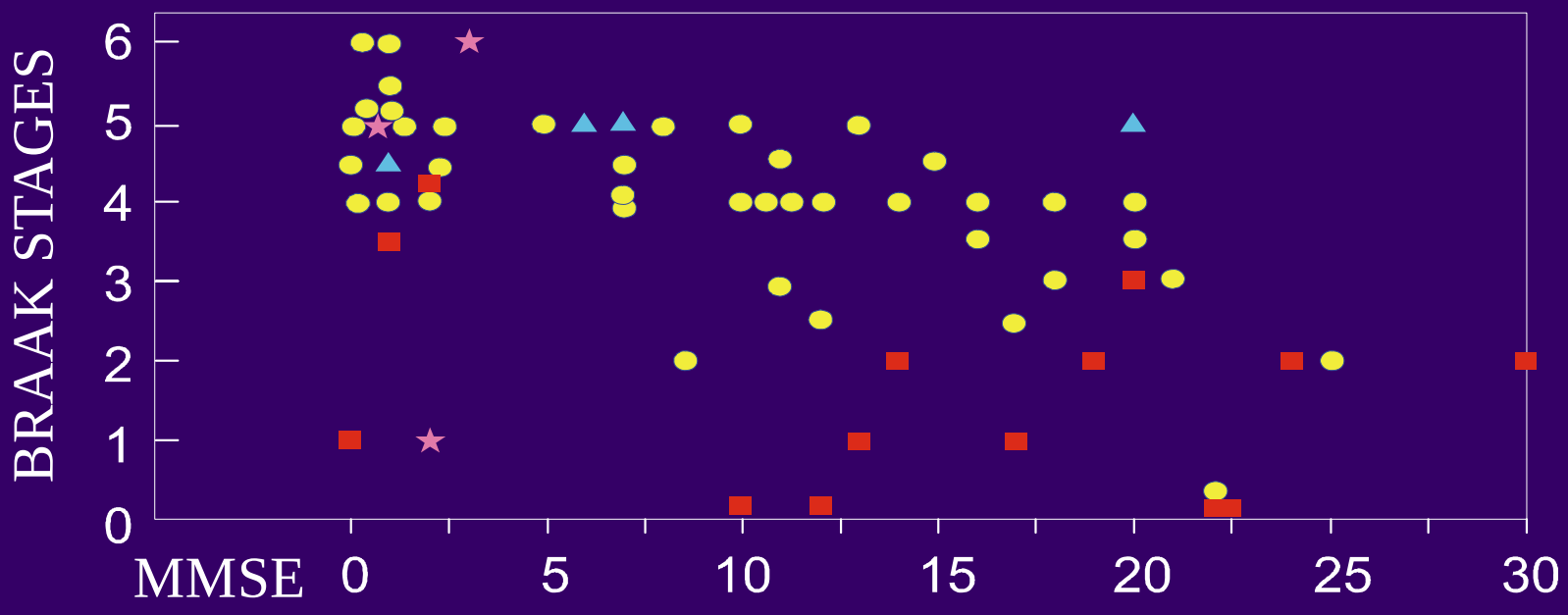
Brains of aged subjects without cerebrovascular lesions (n = 112)



DLB (n=17)
Plaque type AD (n = 4)

r = 0.756; df = 112; P < 0.0001
mean age 79.7 ± 8.5 years

Brains of aged subjects with cerebrovascular lesions (n = 61)



with CV lesions
"pure" vascular dementia
MIX type dementia
hippocampal sclerosis

Ischemic-vascular and mixed dementia

Comparison of AD, MIX and IVD(n) shows the following:

Disorder	Braak stage	Final MMSE	Stroke history
”Pure” AD (291)	5.2	2.1	9.8%
AD+lacunar state (67)	4.7	6.8	21 %
AD+old inf.(</>10ml)(22/20)	4.6/4.7	8.8/8.5	33/95%
AD+hippocamp.scler. (16)	4.6	5,6	?
MIX (AD+CVD <30-50ml) (7)	4.5	4.0	95%
”Pure” IVD (82)	1.8	8.2	> 90%
SAE/MIE (35/30)	1.7/1.6	12/13	95/100%
SID (14)	1.0	4,6	98%

These data confirm other studies that small CVLs have little impact on cognitive decline in severe AD, although there are slightly lower AD stages and more infarct history in AD with than without CVLs which may ”unmask” or promote dementia in less severe AD.

Density of AD lesions in patients (with and without vascular lesions) with a similar average degree of severity of clinical dementia

	Vascular lesions		
	Present	Absent	*P*
Aß FD (ST)	2.2 (3.3±3.4)	12.6 (12.2±6.5)	0.0030
NFT (ST)	2.6 (10.6±15.1)	39.7 (39.9±14.9)	0.0030
SP (ST)	3.3 (4.6±5.3)	24.2 (23.1±8.2)	0.0005
Aß FD (MF)	0.8 (1.5±1.9)	11.0 (10.4±4.3)	0.0005
NFT (MF)	3.3 (4.6±5.3)	19.9(19.7±6.2)	0.0010
SP (MF)	0.8 (2.5±4.3)	14.2 (16.7±7.9)	0.0010

Zekry et al, ANP 103: 151, 2002

Types and location of cerebrovascular lesions in vascular dementia (total 131)

1) Multiple infarcts (38)

ACM bilateral 5

ACM left/right 6/2

ACM bilat. + ACPS/ACPD 2/1

ACMS + ACPS 2

ACMD + ACPD 1

ACP bilateral 2

ACP left/right 3/1

ACAS + ACMS 1

multiple bilateral. 10

multiple left hem. 2

2) SAE (subcortical) (72)

Basal ganglia 41

Basal ganglia + white matter. 24

Basal ganglia + thalamus 7

3) SID / strategic infarcts (21)

Thalamus bilateral . . . 9

Thalamus left 2

Thalamus + hippocampus 10

Types and location of cerebrovascular lesions in mixed dementia (total 64; personal series)

1) AD+Multiple infarcts (41)

ACM bilateral 5

ACM left 8

ACM right 3

ACM + ACA bilat. 1

ACM + ACP left 2

ACM + ACP right. 1

ACM + ACP left/right. . 3/3

ACM bilat. + ACPD. . . . 1

ACP bilateral 1

Multiple cortical and subcortical bilateral . . 9

Multiple left hemisphere . 4

2) AD+SAE (subcortical) (19)

Lacunes basal ganglia 8

" " " + white matter . 6

" " " + thalamus . . . 5

3) AD+SID / strategic infarcts (4)

Thalamus bilateral . . . 2

Thalamus + hippocampus. 2

Type and location of infarcts in AD + minor CVD

Infarct and location (total more than 100 %)	Lee et al, 2000 (n=36)	%	Personal series (n=106)	%
Cortical microinfarcts	18	50	21	20
Lacunar infarcts:				
Basal ganglia	18	50	43	40
Thalamus	15	40	16	14
Basal ganglia + thalamus	6	16	15	14
White matter	3	8	3	3
Multiple infarcts (cort. + subcort.)	6	16	8	8

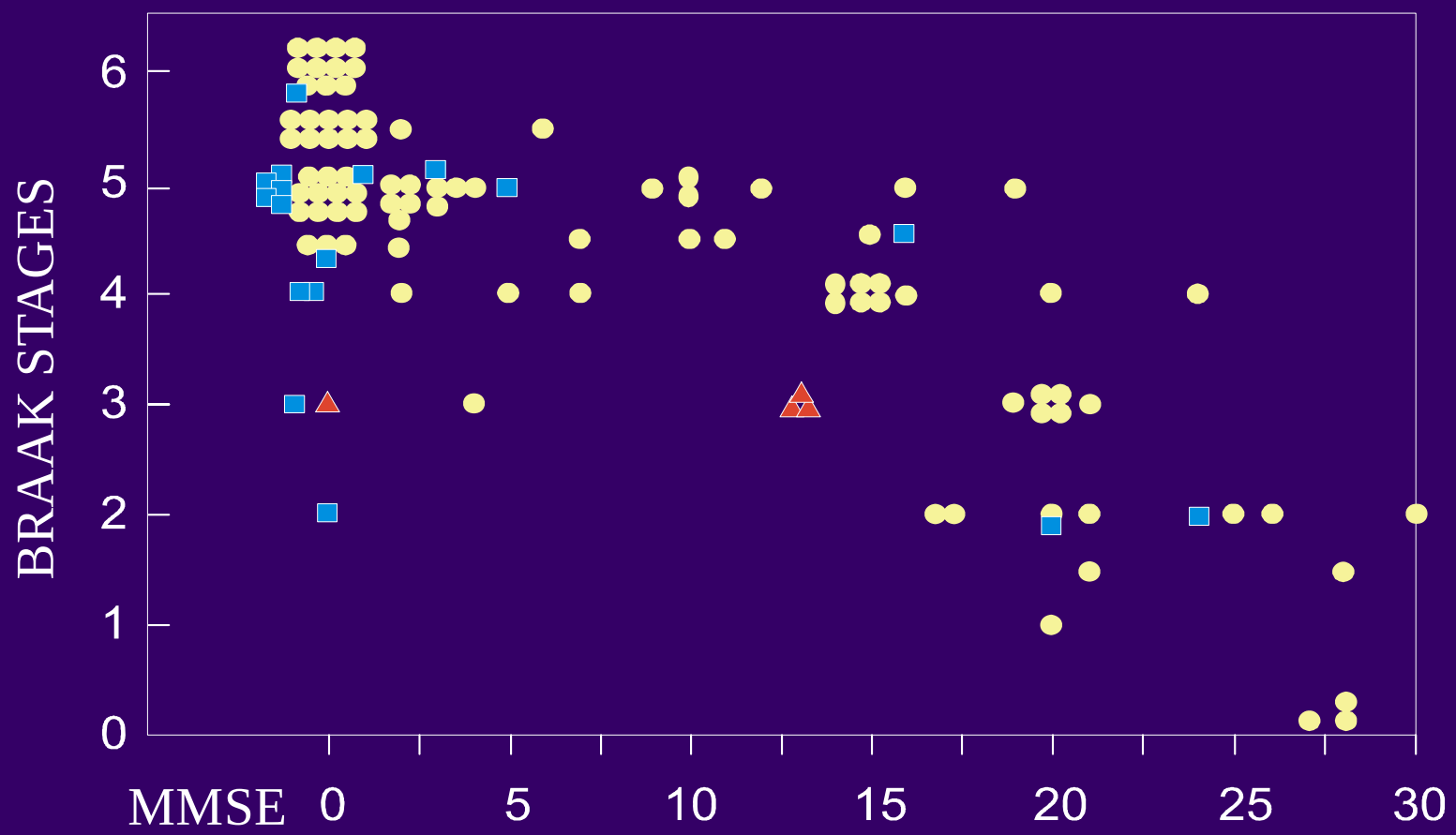
Relation between cognitive state and pathology

Comparison of AD. MIX and VaD shows the following:

Disorder (n)	Age at death	Braak stage	Final MMSE (n)	Stroke history %
”Pure” VaD (82)	79.7±6.9	1.5	10.5 (33)	97
SAE/SID (38/16)	79.0/77.0	1.6/1.3	13/9.0 (25)	98-100
MIE (30)	83.1±9.4	1.6	9.5 (8)	100
MIX (AD+CVD) (48)	82.7±5.9	4.8	7.3 (14)	95
AD+Hippocamp. scler. (26)	82.8±6.7	4.8	4.1 (10)	NG
AD+lacunes/ old infarcts <10ml (133/25)	83.2/84.6	4.0/4.8	6.0 (45)	21/33
”Pure” AD (400)	80.3±8.9	5.2	1.3 (80)	10

$p < 0.001$ vs AD; $p < 0.001$ vs other groups

Brains of aged subjects without cerebrovascular lesions (n = 112)



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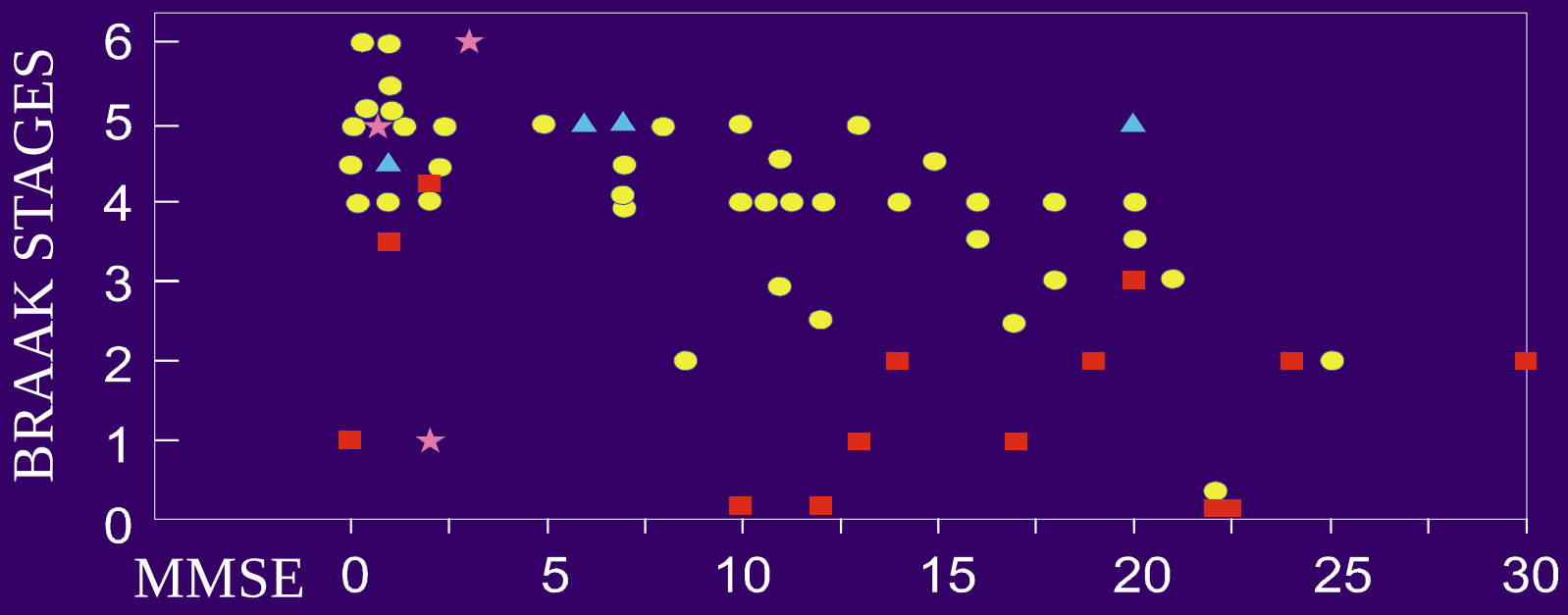


with CV lesions
"pure" vascular dementia
MIX type dementia
hippocampal sclerosis

Common lesions in AD, VaD, MIX, and aged controls

Pathological feature *[%]*	AD	VaD	MIX	Aged controls
Cerebral amyloid angiopathy	98	30	~ 90	23-45
Small vessel disease/ MVD	~ 50	> 50	> 50	~ 20
Total infarctions	10-20	100	30-40	> 10
Microinfarcts/ lacunes	30-46	70	60-70	17-21
Intracerebral haemorrhage	10-15	15	10	1-2
White matter pathology	40	80	70-80	< 20
Loss of cholinergic markers	75	40	~ 70	
CVD/ atherosclerosis	45-60	60	~ 60	30-53

Kalaria, 2003; Jellinger, 2005

Postmortem Examination of Vascular Lesions in Cognitive Impairment .

A Survey among Neuropathological Services .

Pantoni, Sarti, Alafuzoff, Jellinger, Munoz, Ogata, Palumbo. Stroke 2006, 37: 1005.

A full appreciation of cerebral vascular lesions in cognitively impaired patients can only be reached at the neuropathological level. However, there are no detailed guidelines regarding what neuropathologists should look for at autopsy in cases of suspected vascular dementia / cognitive impairment. We surveyed the postmortem neuropathologic procedures used in 13 centers in examining lesions of presumable / possible vascular origin in cognitively impaired.

A large variability across centers was observed in the examination procedures and histology techniques. Heterogeneity existed also in the definition of commonly found lesions (eg, white matter alterations, small vessel disease), interpretation of whether or not the lesions were of vascular origin, and in the interpretation of the cause of cognitive decline.

Harmonization of neuropathologic procedures is needed in the field of vascular dementia / cognitive impairment to better understand the association between various vascular lesions and cognitive impairment.

Key variables to define the pathology of VaD

- Identify as ischaemic or haemorhagic infarct(s)
- Presence of lacunes and lacunar infarcts: etat lacunaire (grey matter) and etat crible (WM)
- Location of infarcts: cortex, WM, basal ganglia, brainstem, cerebellum
- Circulation involved: arterial territories - anterior, middle or posterior
- Laterality: right or left anterior and posterior
- Sizes and number of infarcts=dimension: 0–4, 5–15, 16–30, 31–50 and >50 mm; if size <5 mm, determine as small or microinfarcts
- Presence and location of small vessel disease: lipohyalinosis; fibrinoid necrosis; CAA
- Presence of white matter disease: rarefaction or incomplete infarction
- Degree of gliosis: mild, moderate or severe
- Presence of Alzheimer pathology (including NFT and neuritic plaque staging). If degree >stage III, the case is mixed AD and VaD
- Presence of hippocampal sclerosis

Each of the above features can be scored numerically to provide a summary. For example, 0 absent and 1 present, or using a grading system. Less frequent lesions including watershed infarcts and laminar necrosis may be scored similarly. Increasing numerical value may also be assigned to the infarcts.

Pathogenesis of cerebral changes in hypertension

Hypertension → **↑ Intraluminal pressure** ← **↑ Circulating vasoconstrictors**

Abrupt BP ↑ → **Forced vasodilatation** (breakthrough of autoregulation)

BBB breakdown

Stages of BBB breakdown

Stage I → **Localized** focal edema

Stage II → **↑ Macrophages, astrocytes, and smooth muscle cells** + **Necrosis**

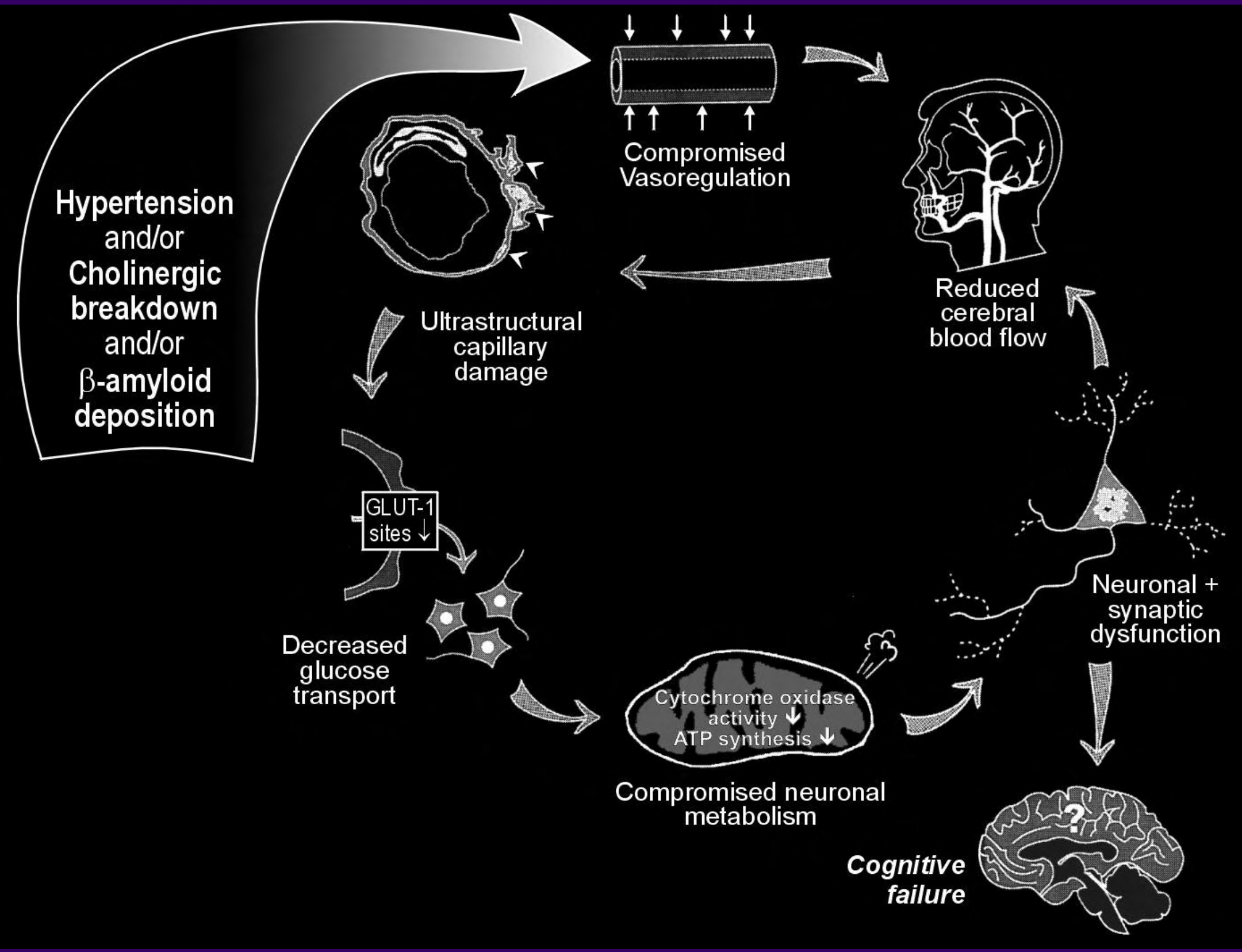
Stage III → **Remote focal necrosis** (lacune)

Multiple → **Cognitive impairment, dementia**

Widespread diffuse cerebral edema → Hypertensive encephalopathy

Anti-Ht Rx → **Survival**

Death



Modified from Karkas & Lutten, 2001

Pathogenic factors in the development of mixed dementia

Risk factors

aging, genetics, hypertension, hypercholesterinia

AD pathology

plaques, tangles

synapse loss, neuron loss

amyloid angiopathy

Cerebral infarcts

Status lacunaris White matter lesion

Multiple microinfarcts

Brain atrophy

Cognitive deficit Dementia

Vascular pathology

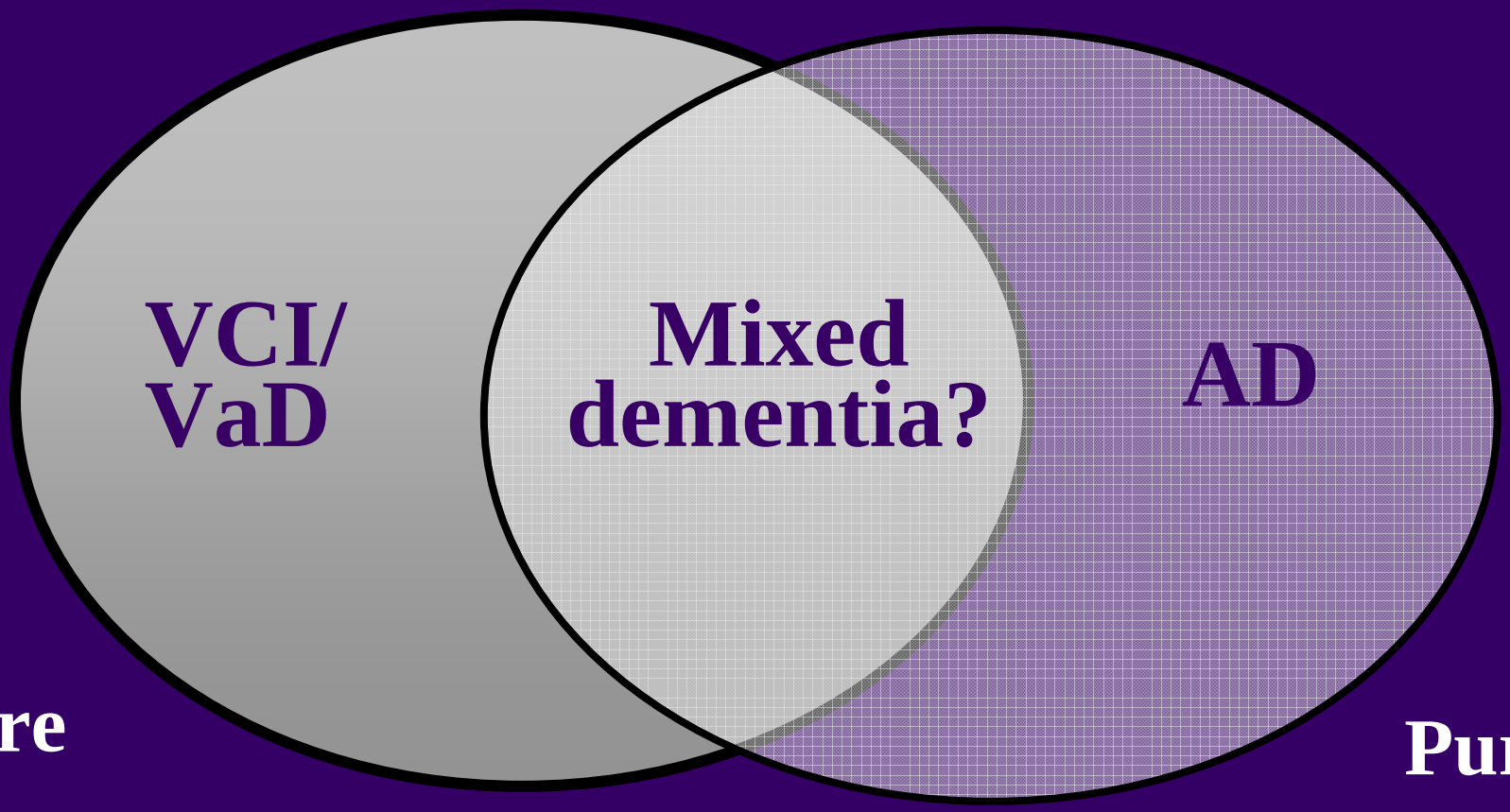
atherosclerosis, macro-, micro-angiopathy

decreased perfusion

decreased glucose metabolism

cerebral embolism

VaD and AD – Overlap



Pure
VaD / MID?

Pure AD?

Even Auguste D exhibited
CBV pathology

"…clinically diagnosed VaD …87% AD either alone (58%) or with cerebrovascular disease (42%) (mixed- neurodegeneration)…"
(Nolan et al, 1998)

Summary

Mixed dementia (MD) refers to a combination of definite Alzheimer disease (AD) and vascular encephalopathy, but due to considerable overlaps the distinction between both disorders is controversial.

There are strong associations and synergistic effects between AD and cerebro(micro)vascular changes. For clinicial diagnosis of MD the clinical/neuroimaging criteria of possible AD plus CVD as separate disorder are used.

We proposed the combination of autopsy-proven AD with multiple vascular lesions in cerebral cortex, basal ganglia, thalamus, hippocampus and/or white matter with about 30-50 ml of infarcted brain volume. Generally accepted and validated histopathological criteria for the diagnosis of VaD and MD are currently not available and causal relations between brain lesions and dementia are unclear. The population-based prevalence of MD is unknown. In retrospective and prospective autopsy studies, it ranges from 2 to 58% with reasonable means of 6 to 12%.

Summary II

In a consecutive autopsy series of 1100 demented elderly subjects and 660 probable AD patients in Vienna, Austria, 38-43% showed "pure" AD, 8-9% atypical AD, 23-29% AD plus vascular lesions, 10% AD plus Lewy body pathology; MD was diagnosed in 4.5 and 1.8%, "pure" VaD in 8.5 and 4%, respectively.

Like the MRC-SFAS and other studies, this indicates frequent coexistence of AD with multiple cerebrovascular lesions in demented patients. In both AD and VaD most concomitant vascular lesions involve subcortical regions (basal ganglia, thalamus, white matter) or are multiple microinfarcts, whereas in MD, large infarcts and multiple microinfarcts were more frequent, suggesting different pathogenic mechanisms in early/mild AD. Critically located small vascular lesions may induce/promote cognitive decline, but in full-blown AD they appear of minor importance.

The major pathogenic factors inducing AD, VaD and MD are discussed and suggest synergistic relations between these disorders. However, currently available morphological criteria for AD and VaD are of limited value for the diagnosis of MD, and more distinct and critically evaluated clinico-pathological criteria are warranted.