

CADASIL: Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy

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Abstract. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a recently identified cause of stroke and vascular dementia. It is a condition of mid-adulthood due to mutations of *Notch 3* gene on chromosome 19. Whereas the disease was first reported in European families, since 1993 CADASIL has been observed in American, African and Asiatic pedigrees, suggesting that today, the disease probably still remains largely underdiagnosed. The pathological data first dealt with the white matter and the basal ganglia showing the features observed in Binswanger's subcortical arteriopathic encephalopathy; over the past few years, CADASIL has become appreciated as a systemic vascular disease with specific features. Here we have reviewed the literature from 1977 to the present for pathologically and genetically verified cases accompanied by relatively complete clinical descriptions so as to give the pathological features associated with this condition a clearer definition. The review will focus mainly on pathological studies and the pathophysiological mechanisms most likely to be involved in CADASIL.

Key Words: CADASIL; Leukoencephalopathy; Notch 3 gene; Vascular smooth muscle cell.

HISTORICAL OVERVIEW

In 1955, Van Bogaert (1) reported that 2 sisters had a "subcortical encephalopathy of Binswanger's type of rapid course" with onset during mid-adulthood. They presented with dementia, gait disturbances, pseudobulbar palsy, seizures, and focal neurological deficiencies. Two other sisters died at 36 and 43 years old after progressive dementia. The father had a stroke at age 51 and died later from a myocardial infarct. The neuropathological aspects of the parenchymatous brain lesions were relatively constant with a subcortical topographic expression. The arteriosclerotic etiology of the disease was emphasized as in a previous report by Mutrux (2). The concept of "multi-infarct dementia" was introduced by Haschinski et al in 1974 (3) in place of the earlier term "arteriosclerotic dementia." In 1977, several families suffering from an autosomal dominant stroke condition of unknown etiology were reported under various names such as "hereditary multi-infarct dementia" (4, 5) or "familial sclerosing vasculopathy" (6). These authors were the first to describe a familial cerebrovascular disease particularly affecting leptomeningeal and deep cerebral small arterial vessel regions, reporting the thickening of the vessel walls that caused a reduction of their lumen and a probable occlusion. Up to 1993, several similar families were reported using numerous eponyms: "Chronic familial vascular encephalopathy" (6), "Familiäre zerebrale Arteriosklerose" (7), "Familiäre zerebrale Gefäßerkrankung" (8), "Hereditary Multi-infarct Dementia" (9), "Demence sous-corticale familiale avec leucoencéphalopathie artériopathique" (10), "Familial disorder with Subcortical

ischemic strokes, dementia and leukoencephalopathy" (11), and "Slowly progressive familial dementia with recurrent strokes and white-matter hypodensities on CT-scan" (12). Because of the confusion raised by all these different names, the acronym of CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy) (13) was proposed to designate this disease that the authors had previously reported as "Autosomal dominant syndrome with stroke-like episodes and leukoencephalopathy" (14). The acronym highlights the main characteristics of the disease. Furthermore, it was demonstrated that the gene was located on chromosome 19 in the first family (13), immediately confirmed in a second French pedigree (15). At the same time, new pathological studies showed that brain vascular features presented a peculiar ultrastructural aspect. A granular osmiophilic material (GOM) was described by Baudrimont (16) in the leptomeningeal and white matter vessel walls. Since 1993, it has been possible to use skin biopsies for analysis to find this GOM in the vessel walls, as the disease has been identified as a systemic condition (17, 18). In 1996, the application of epidemiological, genetic, clinical, and skin pathological correlative studies has allowed us to demonstrate that various mutations of *Notch 3* gene are responsible for the disease (19). With this major step forward in the understanding of CADASIL, genetic testing could be used for diagnosis. Furthermore, this discovery added to the use of skin in research will help us to understand the pathophysiology of the disease and in the future open up the possibility of a more therapeutic approach.

Clinical Presentation

This review focuses essentially on pathological studies and the pathophysiological mechanisms most probably involved in CADASIL. Thorough reviews have been

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TABLE 1
Macroscopy and Histology

Authors	Refer- ence	Year	Number of cases	Pedigree	Clinical presentation	Brain	Macro- scopy	Hema- toma	Brain	
									Slight global atrophy	
Sourander	4	1977	4	D	Stroke (4)	4	4	1		
Stevens	6	1977	?	D	Stroke	≥1	1			1
Sonninen	9	1987	1	D	Stroke	1	1			
Estes	45	1991	3	?	Dem (2) Str (1)					
Davous	10	1991	1	D	Stroke + Dem	1	1			
Berthier	33	1992	1	?	Stroke	1	1			
Baudrimont	16	1993	1	D	Seizure, stroke	1	1	1		
Gray	31	1994	1	D	Dementia	1	1			1
Zhang	36	1994	3	D	Stroke (3)	3	3			
Gutierrez-M	32	1994	1	D	Stroke + Dem	1	1			
Jung	37	1995	1	D	Stroke	1	1			
Lammie	38	1995	2	D	Stroke (2)					
Ruchoux	18	1995	1	D	Dementia	1	1			1
Ragno	35	1995	1	D	Stroke	1	1			
Sabbadini	44	1995	1	D	Stroke					
St. Clair	43	1995	2	D	Dementia	2	2			
Malandrini	34	1996	1	D	Migraine + Stroke	1	1			

D = Dominant. Str = Stroke. ? = Lack of data. 3 = Cases already published. Dem = Dementia. + = Present. 1 or 2 = Number of patients examined.

published previously on general or neurological aspects of CADASIL (20–22), and the reader is encouraged to refer to these reviews for further information. The initial symptoms vary, but include strokes (85%), dementia (30 to 90% depending on the age of observation), migraine with aura (30%), and severe mood disturbances (20%). The mean age of onset is 45 years, irrespective of gender. The duration of the disease varies between 10 and 30 years. The main clinical presentation of CADASIL is recurrent subcortical events, either transient or, more often, permanent. However, the vascular presentation is not constant and various other symptoms can occur. The dementia is characterized by frontal lobe symptoms and memory impairment. The cognitive impairment occurs step by step and is associated with recurrent stroke events and with neurological signs such as pseudobulbar palsy, gait disturbances, pyramidal signs, and sphincter incontinence. The dementia satisfies all the criteria for vascular dementia (22, 23). Attacks of migraines with aura is the earliest clinical manifestation, occurring at a mean age of 30 (24), but occasionally even before the age of 20 (21, 22, 25). These migraine attacks may be caused by repeated ischemic episodes or by an underlying vascular disorder leading to white matter abnormalities (25). Severe mood disturbances are noted and are extremely variable between families (22). Such manifestations correspond to a severe depression of the melancholic type, sometimes alternating with typical manic episodes, which

are probably secondary to ischemic lesions of caudate and lentiform nuclei (26).

Laboratory Investigations

CSF examination is usually normal; however, oligoclonal bands (in 2 patients) and a pleiocytosis (in 1 patient) (22) have been found. No vascular risk factors are present, and investigations must rule out all known sporadic or hereditary causes of cerebral ischemia: coagulopathy, MELAS syndrome (mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes), Fabry's disease, abnormal lipoproteinemias, cerebral amyloid angiopathy, and homocystinuria. Electromyogram examination is normal. In the first family described, an immunoglobulinopathy was noticed in 2 cases, but is never found in other affected pedigrees (14).

Neuroimaging

MRI is always abnormal in symptomatic patients, but signal abnormalities have been detected as early as age 20 (21, 24, 27). The T2-weighted images show punctated and nodular hypersignals with a symmetrical distribution; these predominate in periventricular areas and in the centrum semi-ovale, but are also found in the basal ganglia and in the pons. CT scan can reveal the white matter and basal ganglia lesions, but is much less sensitive than MRI (20). Consequently, MRI is an essential tool for the genetic study of CADASIL. For more in-depth information,

TABLE 1 (Continued)

Brain										Vessels analyzed				
Cerebellar atrophy	Leukoencephalopathy	Basal ganglia infarcts	Cerebellar lesions	Mesencephalic & pons infarcts	Brain biopsy	White matter	Meningeal	Retina	Heart	Kidney	Visceral arteries & aorta	Large vessels		
+	+	+			1	1			1					
+	+													
+	+				3	3	3							
+	+				1	1	1							
+	+				1	1	1		1					
+	+				1	1	1		1					
+	+				1	1	1				1			
+	+		+		1	1	1			1				
+	+		+		2	2	2							
+	+		+		1	1	1		1			1		
+	+		+		1	1	1		1			1		
+	+		+		1	1	1		1			1		
+	+		+		1	1	1		1			1		

TABLE 2
Reports Concerning Peripheral Biopsies Only

Authors	References	Year	Number of cases	Pedigree	Clinical presentation	Muscle	Nerve	Skin
Ruchoux	17	1994	6	D	Stroke (6)	6		2
Schroder	46	1995	1	D	Stroke + Dem		1	
Lechner	49	1996	1	D	Dem + Stroke		1	
Furby	59	1997	1	D	Stroke			1
Ruchoux	50	1997	7 + 3	D	Migraines (3)	7		3 + 3

D = Dominant. Dem = Dementia. 7 = Cases already published.

the reader may refer to recent specific reviews (21, 27, 28). Cerebral angiography was normal in most of the patients analyzed, except in 1 case with a noticeable narrowing of small arteries (22). A worsening of the neurological status of 2 CADASIL patients has been reported after angiography (29). Only 1 demented patient with severe basal ganglia lesions showed a decrease of cortical metabolism in a positron emission tomography study (30).

Genetics

Tournier-Lasserre et al (13) performed genetic linkage analyses in 2 unrelated families and assigned the disease locus to chromosome 19q12. Then, analysis of additional pedigrees with new microsatellite markers allowed them to refine the locus assignment within a 2cM interval (15). Afterwards, mutations of *Notch 3* gene were shown to be the cause of CADASIL (28). The whole genetic linkage analysis was done thanks to the use of the neuroimaging

results added to the clinical status of the family members. The reader may refer to these reports for complementary data (14, 15, 19).

PATHOLOGICAL REVIEW

Twenty-two reports concerning 35 suitable patients have been included in this review. Data concerning these reports is summarized in Tables 1 and 2.

Gross Appearance

Seventeen brains studied (Table 1) were unremarkable except for a slight and uniform atrophy, predominant in some areas: frontoparietal (31, 32) and cerebellar in 2 cases (18, 32). Two brains had massive hematomas (4, 16). Exceptionally, the circle of Willis might show patchy and mild atheromatous or arteriosclerotic changes without vessel obstructions (32, 33). In the first gross description of 4 brains, Sourander and Wallinder (4) described the general pattern visible to the naked eye as strikingly

uniform. In accordance with them, subsequent authors (Table 1) described multiple small necroses and post-necrotic cystic lesions, particularly involving the periventricular white matter, basal ganglia, thalamus, mesencephalon and the pons. The cerebral white matter is grayish-brown or granular with multiple small cystic lacunae that may be extensive and confluent. Most often the subcortical white matter is better preserved. An obvious ventricular dilatation is noted.

Gross examination of the other organs was reported in 10 cases (4, 16, 18, 31, 32, 34-36) and was unremarkable except for rare cases showing atheromatous plaques in the coronary arteries (4, 36) and aorta (18, 36).

Brain Histology

Sourander (4) gave the autopsy record on histologic brain findings in only 3 of his 4 cases and Sonninen (9) had no available histological data; thus, only 15 brain histological reports are included. Six other living cases with informative cerebral biopsies have been added (Table 1). Histologically, a diffuse and focally intensive pallor of myelin staining (Fig. 1A) is observed throughout the white matter, partially preserving the subcortical U-fibers. In the deep areas of the white matter and in the internal and external capsules, there are multiple infarcts at different stages of development with macrophage reactions, cavitation, and mild or moderate diffuse gliosis. The corpus callosum may be involved. In the diffusely demyelinated areas, there are few sudanophilic fat granules. Destruction and degeneration of the nerve fibers almost parallels the severity of demyelination. These lesions are nearly symmetrical in both hemispheres, and are most conspicuous in the frontal, parietal and occipital lobes. Lacunar infarcts in the basal ganglia and thalamus have been invariably reported. Similar lesions are present in the mesencephalon and pons, where longitudinal tracts show pallor of myelin and where some infarcts are described (6, 18). Most of the cerebral cortices are described as being free

of lesions, with few or no plaques, no DNF, and no amyloid deposits, but some authors mention rare foci of neuronal rarefaction and fibrillary gliosis (18, 34). A widely spread "ischemic cell change," diffusely distributed in the third cortical layer of the frontal and temporal cortex, is reported in 2 cases (4) and an "aspect lacunaire" is found in the cortical areas mainly at the junctions between the sixth layer and the adjacent white matter in our case (18). Interestingly, an exceptional case (31) shows diffuse senile plaques throughout the entire neocortex, characteristic of Alzheimer disease without amyloid angiopathy. This case clinically and pathologically overlaps with Alzheimer disease. No cerebellar lesions were noticed except a slightly reduced population of Purkinje cells, a slight gliosis in the white matter, and a laminar spongiosis localized next to the Purkinje layer in our case (18).

Vessel Alterations

Consensus authors have pointed out the salient vascular changes: thickening of the white matter and meningeal vessel walls with a peculiar smudged fibrohyalin aspect. Table 3 summarizes the vessel changes. In 3 cases, Sourander (4, 5) described widely distributed occlusive vascular changes with subendothelial fibrous proliferation of smudgy hyaline degeneration within the intima, duplication-fragmentation of the internal elastica lamina, and sparse perivascular infiltration with chronic but rare polynuclear leukocytes. In 2 of his cases, some vessels are occluded and fibrinoid necrosis of the intima is present. Rare fibrinoid deposits are noted in 2 other cases (6, 18), and sparse perivascular inflammatory cells are also found in 6 cases (16, 18, 33, 34, 37, 38). These fibrinoid and inflammatory changes most probably correspond either to a focal evolution of the disease or to interfering features of another disease. The smudgy and granular aspect of the media with a striking loss of muscular nuclei and the presence of a few globular cells or scattered ballooned muscle cells with a clear cytoplasm

↑

Fig. 1. A: Coronal section of the left cerebral hemisphere through the posterior part of the thalamus and the commissura posterior. There is diffuse mild atrophy and a diffuse pallor of the white matter partially sparing the U-fibers. Laminar subcortical type-1 lacunae are seen at the junction between the cortical sixth layer and the subcortical white matter. Microcystic infarcts are noticed in the basal ganglia and in the capsula interna. (Luxol fast blue, Klüver-Barrera method). B: Cortical arteriole ($\times 250$). C: Retinal arteriole ($\times 250$). D: Meningeal arteriole ($\times 400$). The granular material is readily visualized with toluidine blue staining. A ballooned VSMC nucleus (arrow) is surrounded with granular material in D. E: α -actin immunostaining showing the marked loss of muscle filaments within the inner part of a kidney arteriole wall ($\times 250$). F: Some ballooned cells are clearly stained with α -actin and correspond to the remaining VSMCs ($\times 400$). G: Magnification showing 2 clear ghosts of VSMCs and another containing a nucleus. Granular material is seen surrounding the round cytoplasm (PAS staining $\times 1000$). H: White matter arteriole. The nuclei are surrounded with a clear halo corresponding to the VSMC cytoplasm. Smudged and granular material is slightly PAS positive. (PAS staining $\times 400$). I: Electron microscopic study of a ballooned cell. The cytoplasm is clear and empty of organelles. Surrounding the cytoplasmic membrane, GOM deposits are clearly seen. They are osmiophilic close to the membrane and clearer when dispersed. (Double stain with uranyl acetate-lead citrate $\times 10500$). J: Cardiac arteriole. Note a decrease in the number of nuclei. The nuclei are surrounded with a eosinophilic halo corresponding to their remaining cytoplasm. Each VSMC is isolated from the others. (Hematein-eosin $\times 250$. Inset $\times 400$).

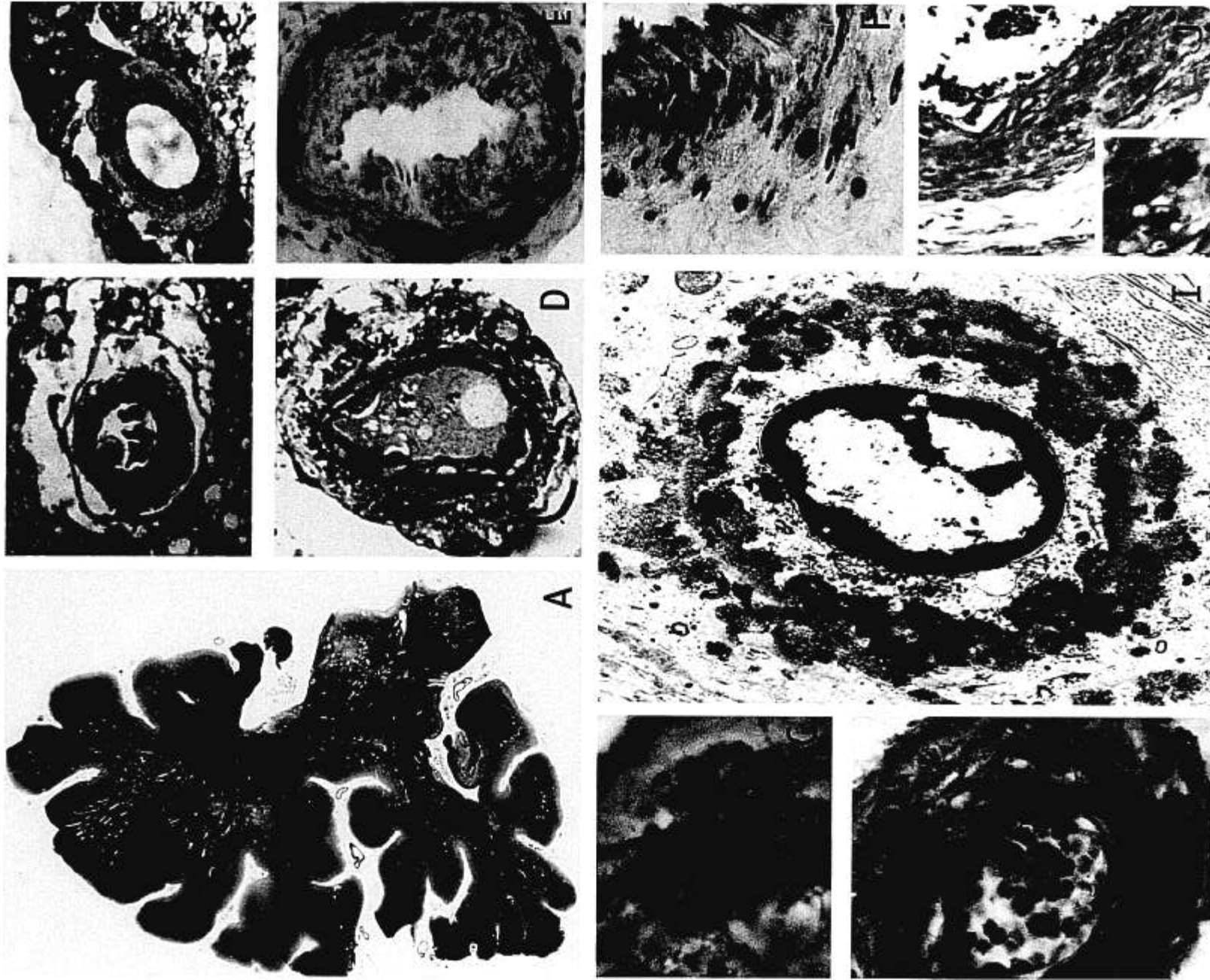


TABLE 3
Histology of the Vessel Walls

Reports	Reference	Year	Number of cases	Hyalin degeneration	Thickened	Smudgy aspect	Granular mat.	Fibrinoid Depos.	Inflammation	Congo Red	Vessel walls	
Stevens	6	1977	B	+	+							
Sourander	4	1977	4B	+	+	+		+	+			
Estes	45	1991	3Bb	+	+	+	+					
Davous	10	1991	1B	+	+	+						
Berthier	33	1992	1B	+	+	+						
Baudrimont	16	1993	1B	+	+	+	+					
Gray	31	1994	1B	+	+	+	+					
Zhang	36	1994	3B	+	+	+						
Gutierrez-Molina	32	1994	1B	+	+	+	+					
Ruchoux	17	1994	6M + 2S									
Schroder	46	1995	1N		+	+	+					
Jung	37	1995	1B	+	+	+						
Lammie	38	1995	2Bb		+	+						
Ruchoux	18	1995	1B, M, S	+	+	+	+					
Ragno	35	1995	1B	+	+	+	+					
Sabbadini	44	1995	1Bb + 2M	+	+	+	+					
St Clair	43	1995	2B	+	+	+	+					
Malandrini	34	1996	1B	+	+	+	+					

B = brain; Bb = brain biopsy; D = diffuse; N = normal; R = red; S = split; - = negative; + = positive; ± = mild.

TABLE 4
Immunohistochemistry

Authors	Reference	Year	Number of samples	Actin	Desmin	Myosin	Tubulin	IgA	IgG	IgM	K	λ	VSMCs	
Estes	45	1991	3Bb											
Baudrimont	16	1993	1B	+	+									
Gray	31	1994	1B					+	+	+				
Zhang	36	1994	3B						+	+				
Gutierrez-Molina	32	1994	1B	<	<									
Schroder	46	1995	1N											
Jung	37	1995	1B	<	<									
Lammie	38	1995	2Bb					l	±	l				
Ruchoux	18	1995	1B-1M	<	<		c	c	c	c				
Ragno	35	1995	1B											
Malandrini	34	1996	1B	+										

B = brain; Bb = brain biopsy; M = muscle; N = nerve; S = skin; A = astrocyte; l = light; - = negative; + = positive; > = more prevalent than the controls; < = less prevalent than the controls; c = same as the controls.

are well described, and the term "small arterial granular degeneration" (SAGRADE) was proposed by Gutierrez-Molina (32). Apart from the granular material (14/21 reported cases), all the other vascular changes observed in CADASIL are invariably present and most prominent in the white matter in Binswanger's subcortical arterio-sclerotic encephalopathy (BSAE) (39, 40, 41). Although

the thickening or thinning of the walls with fibrohyalinosis is constant, a partial or complete occlusion of vessel lumina is relatively rare, but may occur as a consequence of concentric intimal proliferation. In addition, a fibrinoid necrosis may develop in dilated vascular segments; this may result from extravasation of plasma, as suggested by immunostaining for plasma protein using

CADASIL REVIEW
TABLE 3 (Continued)

VSMC		Granular material										Elastica lamina				
Thromboses	Balloon-cell	Loss of nuclei	Basophilic	Toluidine Blue	PAS	Von Gieson	Orcein	Weigert	Masson	Thioflavine	Congo Red	Von Kossa	Perls	Weigert	Von Gieson	Orcein
+	+	+	+	+	+	+	-	+	R	-	-	-	-	-	S	N
+	+	±	+	±	+	±	±	-	R	-	-	-	-	-	S	N
+	+	+	+	+	+	+	-	-	-	-	-	-	-	-	D	N
+	+	+	+	+	±	±	-	-	R	-	-	-	-	-	S	N
+	+	+	+	+	+	+	-	-	-	-	-	-	-	+	S	N

TABLE 4 (Continued)

Vessel walls																		
C3q	Clq	Fibrinogen	Fibronectin	Laminine	Tenascin	Vim	Col-lagen I	Col-lagen III	Col-lagen IV	Col-lagen V	Amyloid component	4G8 Amyloid B	βA4	A	84-5	GFAP	I	
+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+	I
+	+	+	+	+	+	+	+	+	+	+	-	-	-	-	-	-	+	A
+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+	-
-	-	-	-	-	-	-	>	>	>	>	-	-	-	-	-	-	+	-

a computer-assisted 3-dimensional image (42). Thus, this granular material seems to be of outstanding importance, and it is commonly described as eosinophilic (6, 16, 18, 31, 33, 35, 38, 43, 44) and/or slightly basophilic (18, 32, 37, 45).

Histochemistry: This material is dealt with extensively in studies summarized in Table 3. It shows a PAS positivity that is less distinct than the basal lamina staining (Fig. 1G, H). Sourander (4) suggested that the PAS positivity observed in the smudged hyaline media might be

due to acid mucopolysaccharides known to be present in the thickened intima of arteriosclerotic vessels, since after acetylation there is no PAS staining. With Masson trichrom, the granular deposits are red (18, 31, 45). Congo red and thioflavine stains are definitely negative and therefore rule out the hypothesis of an amyloid material. Several authors were impressed by the elastica lamina changes in the white matter, basal ganglia, and meningeal arteries (10, 16, 35, 37, 38, 43) and thought that elastica lamina could be involved. But different elastica lamina

TABLE 5
GOM identification within the Vessel Walls

Authors	Refer- ence	Years	Brain biopsies	White matter	Menin- ges	Periph- eral biopsies	Muscle	Nerve	Skin	General autopsy
Estes	45	1990	3	3	3					
Baudrimont	16	1993	1	1						
Gray	31	1994	1	1		1				
Gutierrez-Molina	32	1994	1	1						
Ruchoux	17	1994				6	6		2	
Schroder	46	1995				1		1		
Lamie	38	1995			1					
Ruchoux	18	1995	1	1	1		1	1	1	1
Malandrini	34	1996	1	1						
Lechner	49	1996				1		1		
Furby	59	1997				1			1	
Ruchoux	50	1997				3			3	

stainings showed that the granular material is elastophilic with Von Gienson staining, but not orceinophilic staining (18, 32, 45). Moreover, in deep cerebral parenchyma, this granular material is observed in small arteriole walls that are lacking in elastica lamina. Perls and Von Kossa stainings are both negative. Guttierrez (32) states that PAS positivity and Alcian blue positivity are attributable to glycosaminoglycan deposition. Finally, the granular material is readily visualized in metachromatically stained plastic sections (brain biopsies and brain samples studied in Epon) (18, 45) (Fig. 1B, C, D).

Immunohistochemistry was done in 16 reported cases including 15 brains, (16, 18, 31, 32, 35-38, 45) 1 nerve (46), and 1 muscle (18) and are summarized in Table 4. Despite the difference of fixation, material, and methods, these studies emphasize 3 findings: (a) The granular deposits are negative for the most common markers of familial cerebrovascular disease and there is absence of any type of amyloid in arterial walls (34, 35, 45). (b) Whereas the divergent immunohistochemical reactions for IgA, IgG, IgM, Kappa, Lambda chains and Complement might account for nonsignificant changes in largely degenerative vessel walls, the normal myosytic filaments (α actin, desmin and myosin) are markedly reduced when compared with control biopsies and corresponded to the remaining ballooned cells and their slender cytoplasms (18, 32, 34, 37) (Fig. 1E, F). (c) The increase in extracellular material well identified by either fibronectin, fibrinogen, vimentin and/or collagen IV (18, 32, 34, 36) is in line with previous histochemical studies that demonstrated the overexpression of the basal lamina and irregular or smudgy elastic tissue. The deposition of extracellular matrix components is probably secondary to VSMC changes. Reactive astrocyte GFAP expression is usually found. Zhang et al (36) emphasized the fact that reactive astrocytes were stained with Endothelin-1, one of the

most powerful vasoconstrictor peptides. However, the astrocytes are found to be stained with endothelin antiserum in other neurodegenerative diseases (47). Consequently, the significance of these findings awaits further studies.

Electron Microscopic Study

Electron microscopic studies, listed in Table 5, have made possible great advances in describing the granular deposits. Estes (45) first observed this granular osmiophilic material (GOM) in the white matter and leptomenigeal arteries of 3 young patients without any family history. Then Baudrimont (16) found similar GOM deposits within the small arteries and arterioles penetrating the white matter and basal ganglia of a patient belonging to the first family described by Tournier-Lasserre. Since then, many authors (Table 5) have reported them and have showed the difficulties in defining their nature. Roentgenographic energy-dispersive spectroscopy of this granular material and of the lysosomes indicates a lack of metallic or mineral components (45). Subsequently, wave length dispersive electron microscopy again confirmed the absence of mineral and metallic components (16). Interestingly, in 1992 we observed GOM deposits within the capillary walls in the muscle biopsy of a patient presenting with a progressive subcortical dementia (18). Therefore, it seemed imperative to check for the possible presence of these GOM deposits in the skin. Their presence in the skin was of great interest for 3 reasons: (a) CADASIL became a systemic disease, (b) the ultrastructural studies of skin-punch could be used as a diagnostic tool, and (c) it was possible to consider a new extracerebral approach for research. Our skin results (17) were similar to nerve biopsy findings by Schroder (46) at the same time.

Systemic Pathological Findings

Consequently, more attention was focused on other systemic vessels in spite of the absence of any other organic signs, except 1 case of myocardial infarction (48). In most of the previous reports, the examination of organs such as the lung, heart, liver, and kidney was unsuccessful in finding similar alterations in blood vessels of any kind. However, a few authors have noted a hyalinosis (18, 36) of spleen arteries or coronaries (16, 18), a moderate to severe nephroangiosclerosis (18, 32, 36), and ballooned muscle cells without granular degeneration in kidney arteries (32). In our case, we found systemic arterial tree vessel changes with ballooned muscle cells surrounded by slightly basophilic blurred hyaline material (18) (Fig. 1E, H, J). The presence of GOM along the entire arterial tree was confirmed by exhaustive ultrastructural studies (18).

The Granular Osmiophilic Material (GOM)

The GOM consists of numerous electron-dense, extracellular granular deposits without filament-like profiles (Fig. 2), ranging in size from very small, barely detectable deposits to large deposits (0.2 to 0.8 μm). They are located close to the vascular smooth muscle cells (VSMC) and are made of 10 to 15 nm granules. The GOM deposits surround the VSMCs without any preferential location at the luminal or abluminal face and are often lodged within large VSMC infoldings. In the infoldings, the cell surface may show multiple caveolae, usually localized in front of the GOM and embedded in the thickened basal lamina. These GOM deposits could either be very dense and close to the VSMC cytoplasmic membrane, or dispersed and less osmiophilic (Fig. 2). Most of the reports concerned brain findings. There is a homogeneity in the descriptions concerning the striking destruction of the VSMCs in the brain-perforating arteries and meningeal arteries. The VSMCs are barely recognizable (Fig. 1I, Fig. 6) both in the white matter (16, 18, 31, 32, 34, 38, 45) and in the cerebral and cerebellar cortices as well as in the optic nerve and the retina (18). Fortunately, the skin, muscle and nerve biopsy studies show the same features but are less marked (17, 18, 42, 46, 49). The first hypotheses advanced were that GOM could be an immunoglobulin (but the lack of immunolabeling ruled it out) or amyloid (but no amyloid or intermediate filaments were visualized and the lack of immunolabeling again ruled it out). It was also hypothesized that there was an eventual secretion related to the presence of numerous caveolae located adjacent to some GOM deposits. But the same accumulation of caveolae was seen at the level of VSMC fragmentation in CADASIL and other diseases. In addition, we found GOM with the exact shape of the outlines of the adjacent VSMC, appearing to be parts detached from the cell and

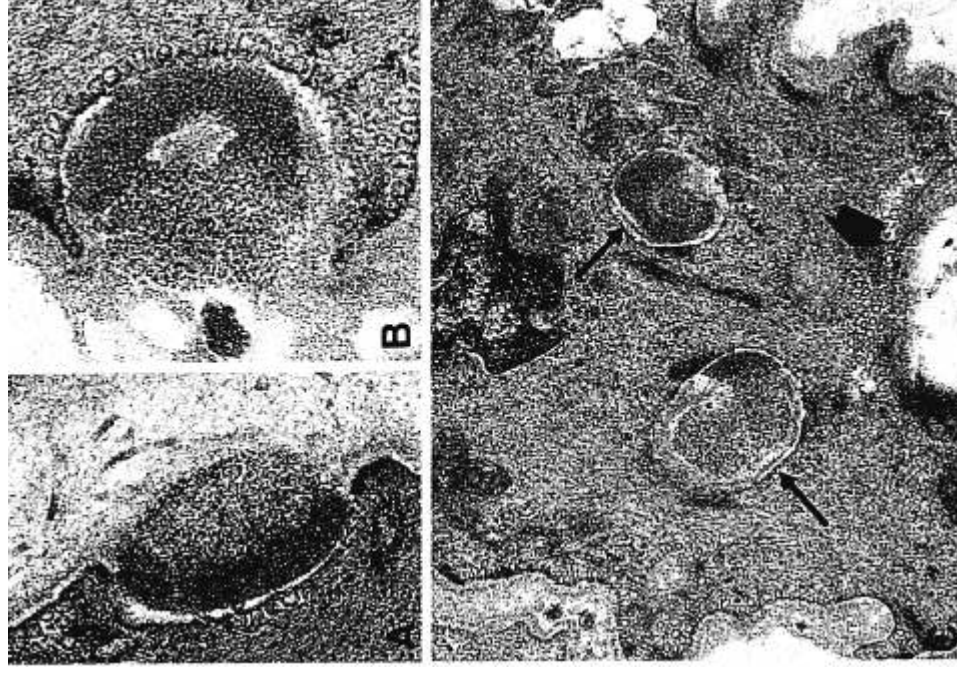


Fig. 2. A, B: Two GOM deposits with a dense part localized close to the cell. The bottoms of the notch are lined with caveolae. The basal laminae are either interrupted or pushed away. (Double stain with uranyl acetate-lead citrate; A, $\times 32,500$; B, $\times 41,500$). C: Formation of GOM patches within a VSMC. There are 3 holes. The smallest hole is just beginning to form (large arrow) with numerous caveolae. The 2 other holes are finished off and are surrounded with rare caveolae. The basal lamina is already recognizable (thin arrow) (Double stain with uranyl acetate-lead citrate ($\times 20,800$)).

resembling puzzle pieces that matched the outlines (Fig. 3). Consequently, the development of caveolae at the close contact between GOM and the surface membrane looked more like a healing process after a loss of material rather than a true feature of exocytosis. Moreover, we noticed that in CADASIL skin biopsies, most of the VSMCs presented a densification of the matrix and a sort of shrinking of the cytoplasm, and we had the opportunity to observe the formation of holes within a VSMC: the bundles of microfilaments disappeared and there was a condensation of granular osmiophilic material (Fig. 2C, Fig. 3). Surrounding this material, a thin dividing area was looming. The more it took shape, the more distinguishable the caveolae became around the GOM. Therefore, an abnormal condensation of the VSMC cytoplasm

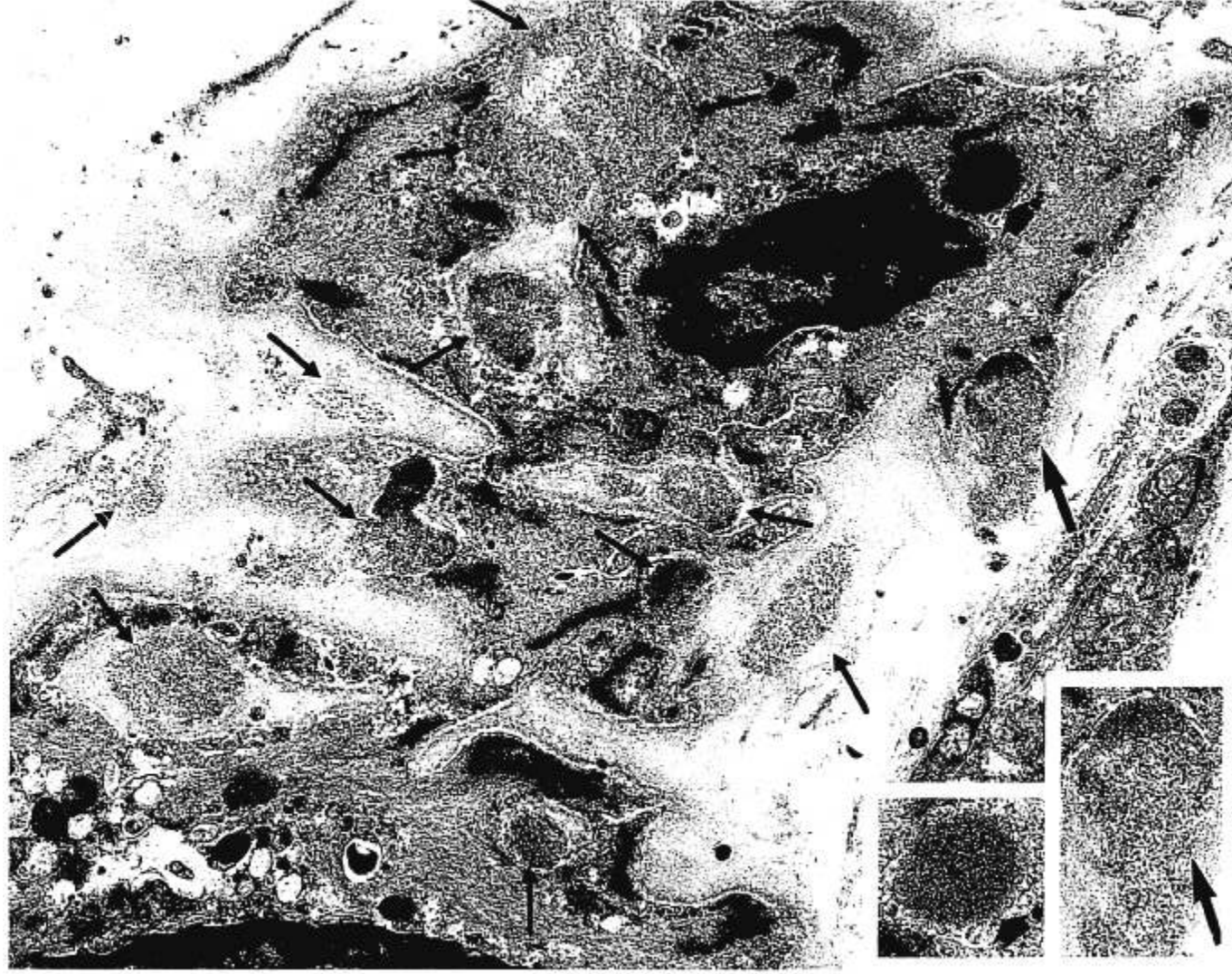
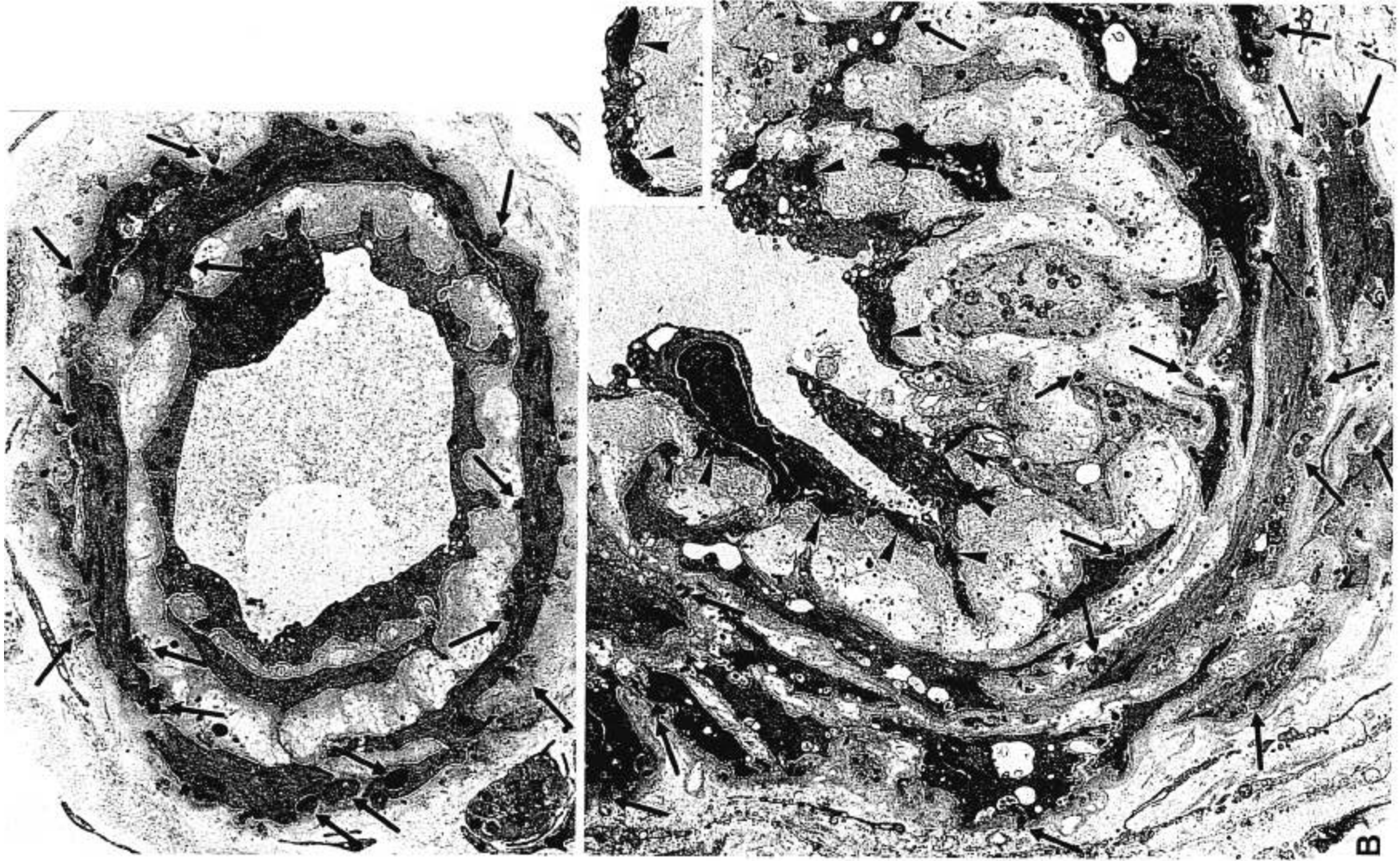


Fig. 3. This VSMC appears to be cut out like a puzzle. Within the cytoplasm, note the numerous holes filled with GOM deposits (arrows) like multiple puzzle pieces. (Double stain with uranyl acetate-lead citrate ($\times 26000$). Inset: Higher magnification ($\times 50000$) showing similar granules located within a new area of densification, probably leading to a new GOM compared with the granules of a GOM localized in a notch.

Fig. 4. A: Junction between capillary and arteriole in skin. The ECs are dense. There is a slight thickening of the basal lamina. Notice the disorganization of the wall with irregularly shaped VSMCs and disruption of the normal VSMC junctions. GOM deposits are observed on both sides of the VSMCs. Some of them are indicated by arrows. (Double stain with uranyl acetate-lead citrate $\times 6,650$). B: Skin arteriole. ECs are condensed with cytoplasm filled with compact bundles of microfilaments (arrowheads) and some clear bubbles. The superficial VSMCs take a radial disposition and have lost their normal junctions. The VSMCs are irregularly shaped and many cytoplasmic notches contain GOM (arrows). (Double stain with uranyl acetate-lead citrate ($\times 3,350$). Inset: with this magnification the bundles of microfilaments are better seen ($\times 5,350$).

CADASIL REVIEW



probably leads to a peculiar granular disintegration that is not as dispersed as it usually is. Is there a decrease in transwall flow? So far, it seems impossible to define the accurate nature of the GOM with certainty.

Variations of GOM Distribution

In the ultrastructural observations, it is the GOM deposits that most attract the authors' attention. So, in our last study (50) we attempted to focus on the endothelial changes and vessel wall modifications depending on the type of tissue. The following section will address these differences.

In the skin, capillaries show fragmented VSMCs and a few barely-recognizable GOM deposits (Fig. 4A). The endothelial cells (EC) are thin, with prominent nuclei that are irregularly shaped with heterochromatin. In skin arterioles the ECs are difficult to identify. Their cytoplasm are extremely reduced and osmiophilic apart from clear bubbles (Fig. 4B). The most striking feature is the abundance of microfilaments organized in compact bundles (Fig. 4B) that probably hinder the normal formation of pinocytotic vesicles (51). The basal laminae are irregularly thickened or duplicated and do not closely follow the adluminal side of the EC. The superficial VSMCs are shrunken and have a more or less radial disposition (Fig. 4). Deeper within the arteriolar wall, the VSMCs are better preserved, but irregularly shaped and surrounded by a thickened basal lamina, which is focally interrupted by GOM (Fig. 4B).

In the muscle and nerve, ECs are swollen, filling the lumen (17, 18, 46, 49, 50). The cytoplasm were clear and contained vacuoles and an enlarged ergastoplasm. The tight junctions seemed preserved in the nerve (17, 18, 46, 49, 50). In muscle capillaries, the VSMCs have often vanished and just a small part of their remaining cytoplasm are surrounded by a large and homogeneous basal lamina frequently interrupted by GOM patches. Areas of striated muscle fiber located close to capillaries show changes of myofibrillary architecture with widespread Z-line streamings and ribosome clusters (18). Within the arteriolar walls, the numerous irregularly shaped VSMCs are surrounded by numerous large GOM patches, often between 5 to 15 around a cell in the muscle (Fig. 5), as well as in the nerve (46, 49). The striated muscle fibers located in front of the arterioles surrounded by several VSMC layers do not present any modifications to the Z-lines. In the oldest patients, ECs had the appearance of lacework. At this state, the ECs did not appear swollen, but were deflated. Only the ghosts of VSMCs are now recognizable with their ring of GOM deposits, and the striated muscle fiber located in front of these altered arterioles showed obvious modifications of the myofibrillar architecture (17).

In small or large arterial walls, the GOM deposits are found either close to the indented or retracted VSMCs or

as opaque and pale deposits diffusing across elastica lamina. The VSMCs seem to have lost most of their cytoplasm to become round or oval with a clear cytoplasm (Fig. 1I), consistent with some histological descriptions of clear round VSMCs surrounded by a halo of a granular material (Fig. 1F-I).

In the brain, despite postmortem alterations of our case, the EC cytoplasm seem either filled with electro-lucent vacuoles of varied sizes bulging into the lumen (Fig. 6A, B), or retracted and osmiophilic and looking like apoptotic cells (Fig. 6C). It is difficult to evaluate the tight junction integrity because we would need to look at several slides in series. But the presence of dark and shrunken ECs seems to correspond to a blood-brain barrier failure. The VSMCs had vanished or only a part of the VSMC cytoplasm was still recognizable because of their ring of GOM patches (Fig. 6). Around the arterioles, large patches of GOM were spreading out, but were held back by the pia matter. Even in the cortex, these vessel modifications led to detachment of the astrocytic feet.

No changes are noticed in any of the parenchyma having sinusoidal capillaries. Similarly, no lesions have been observed in the heart, liver, pancreas, spleen, or, particularly, in the renal glomeruli, because in these tissues endothelia have numerous and wide pores (as does the choroid plexus). However, in these parenchyma, any lesions are strictly located in the arteriole and artery walls. Therefore, the tissues are in no way modified except when in close proximity to arterioles or when they are the result of arteriole wall hyalinosis with its consequences, noticed occasionally in the kidney or in the heart and spleen (16, 18, 32, 36).

Thus, ultrastructurally, CADASIL appears as a systemic vascular disease mostly involving the brain. Apart from the particular granular material seen histologically and the GOM seen by ultrastructure, CADASIL lesions share the same features as BSAE.

PATHOPHYSIOLOGY OF THE MAIN CEREBRAL INVOLVEMENT

Several hypotheses for the pathogenesis of CADASIL have been suggested joining those proposed for BSAE and advanced age (39-41, 52, 53). Currently, the most common consideration of the pathogenesis of BSAE is arteriosclerosis, which preferentially involves the long arteries of the cerebral white matter. Hypertension plays a fundamental role in the development of early vascular changes in small arteries 100 to 500 μ m in diameter, corresponding to medullaris arteries and leptomenigeal arteries, but they are less severe in cortical arterioles (52, 54). Periods of temporary cardiac failure may cause hemodynamic disturbances and poor perfusion of the brain. These phenomena would be more pronounced in the periventricular arterial end and border zones (39, 40). The



Fig. 5. Arteriole in muscle tissue. The ECs are prominent, sometimes filled with a large vacuole (star). The VSMCs are better preserved than in the skin but are surrounded with numerous GOM patches (Double stain with uranyl acetate-lead citrate ($\times 3,600$)).

lesions result from marginal perfusion. The blood flow falls below the level required to maintain normal metabolic functions with resultant death of oligodendroglia and loss of myelin (39, 53). Moreover, the fact that the degree of carotid stenosis does not influence the severity of leucoaraiosis indirectly supports the view that leucoaraiosis is closely linked to disease of small arteries and arterioles (52).

This hypotheses could, in large measure, probably be applied to CADASIL, since the vessel wall alterations are more marked, but in the same locations as in BSAE. No cardiac failure has been reported in CADASIL except in one case (48), but normotension or hypotension regularly recorded in these patients could explain the poor perfusion of these areas. However, some moderately hypertensive patients have been reported having same leukoaraiosis. Nevertheless, one must take the granular deposits into account, and it could be hypothesized that the presence of GOM leads to an increased impediment of essential nutrients. Our last study raises a new point concerning the endothelium, which could be involved in the

pathogenesis of CADASIL (50). The diagram of Figure 7 summarizes these findings. Interestingly, no lesions or slight changes are noticed in the tissues relying on the sinusoidal endothelium. In tissues such as the skin, which relies on an endothelium with gap junctions, only the VSMCs are involved. Bundles of smooth muscle cells are remarkably well preserved as are the adjacent glandular structures. In tissue relying on continuous endothelium with tight junctions such as the skeletal muscle, there are 3 observations: (a) close to a capillary that has just a degenerative smooth muscle cell, the first striated fiber shows Z-streaming as a focal lesion; (b) close to an arteriole with several VSMC layers, the first striated fiber remains normal; (c) in older patients with VSMC layer destruction, the first striated fiber shows severe changes. It seems that the VSMCs have acted as a filter in the second state. In tissue depending on the blood-brain barrier (the brain, optic nerve and retina), the VSMCs are more severely destroyed and even invisible. This does not seem a fortuitous event since it is the only tissue where

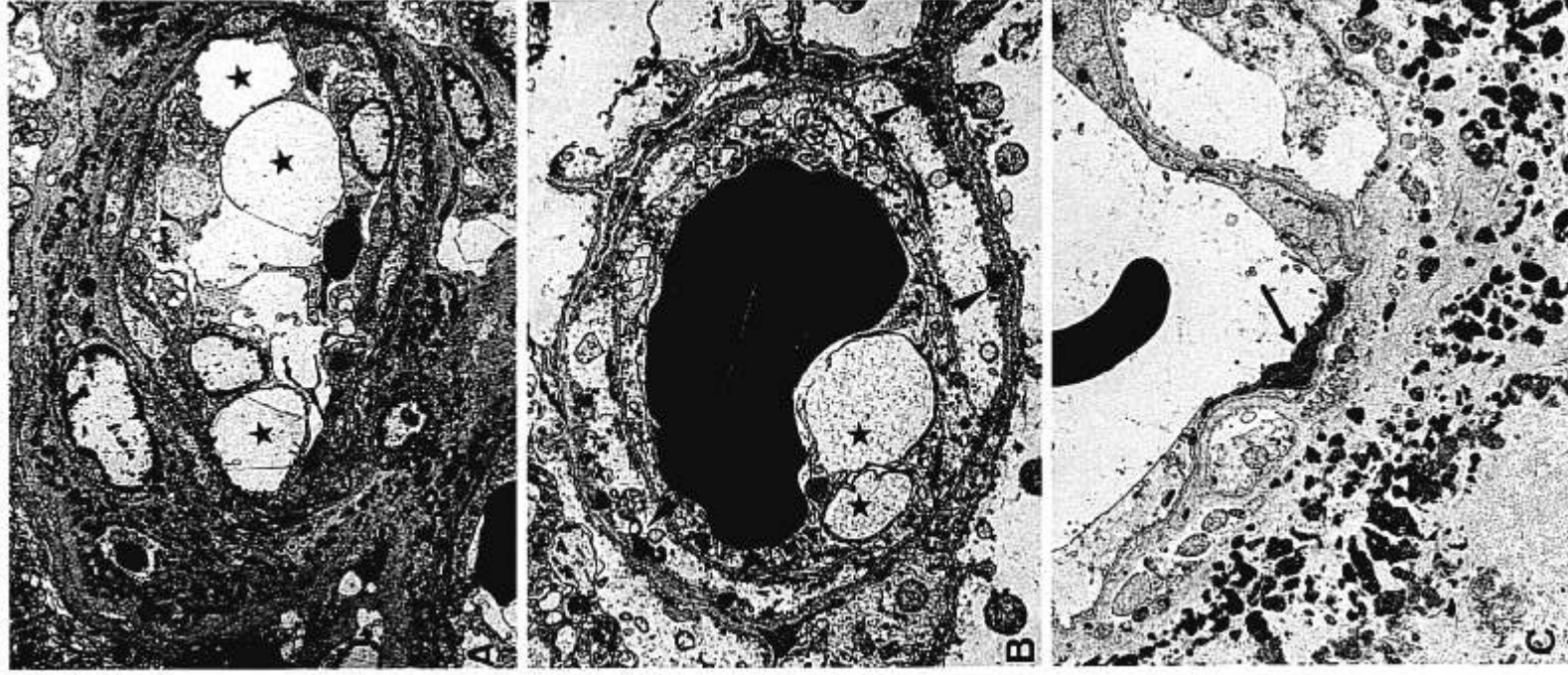


Fig. 6. A: Cortical brain arteriole with 3 bubbles (stars) filling the distorted ECs. The VSMCs are surrounded by multiple GOM patches held back by the pia mater. (Double stain with uranyl acetate-lead citrate, $\times 1,900$). B: White matter capillary showing bubbles (stars) within the EC and dilated organelles. The VSMCs have vanished. Some GOM patches are vis-

ible at the albuminal side (arrowheads). Note the large degree of detachment of the astrocytic feet (Double stain with uranyl acetate-lead citrate $\times 6,150$). C: Perforating arteries. VSMCs are empty and clear. Numerous GOM deposits are spreading away. The endothelium lining shows either clear or dark cells (arrow). (Double stain with uranyl acetate-lead citrate, $\times 5,300$).

all the blood-tissue exchanges are completely dependent on a perfectly working endothelium. Thus, the destruction of the VSMCs might be the consequence of a transendothelial failure. In addition, GOM deposits may hinder the astrocytic foot processes from coming into contact with the VSMCs and jeopardize the integrity of the blood-brain barrier (55, 56), leading to lacunar formation.

Altogether, this data suggests that VSMC involvement and GOM deposits could be the consequence of a decrease in transendothelial transport systems, which might explain why the debris and the GOM are not dispersed in CADASIL as they are in the hypertensive vessel walls. This hypothesis has the distinct advantage of explaining the different lesions according to the type of endothelium and to the different stages observed in the muscle. Nevertheless, this is only an inference drawn from morphological studies.

DIAGNOSIS

Since CADASIL shares a number of features with other cerebrovascular disorders, differential diagnosis is difficult for both clinicians and pathologists. So as not to underestimate the actual frequency of CADASIL-like cases, neuroimaging investigations should be performed on all relatives of patients with CADASIL and on individuals presenting strokes or transient ischemic attacks, severe mood disturbances, and attacks of migraine with aura or dementia, all within an hereditary context. The accurate association of the clinical findings cited above and leukoariosis are crucial because the familial conditions associated with strokes (coagulopathies, dyslipoproteinemias, homocystinuria, Fabry's disease, cerebral amyloid angiopathy, and MELAS syndrome) either have a distinct clinical presentation or have to be ruled out by appropriate investigations. However, leukoariosis is frequently detected in asymptomatic persons over 60 years old and in cognitively impaired individuals, especially those who have evidence of cerebrovascular disorders or risk factors (57). In a large review on leukoariosis, Pantoni and Garcia (52) reported that between 7.5% and 100% of patients with Alzheimer disease have leukoariosis, but that it is generally less severe than that of patients with cerebrovascular disorders, and that an increased prevalence of leukoariosis has been recently described in a variety of psychiatric disorders. They also reported that in addition to cognitive impairment, gait disturbances, a tendency to fall, extensor plantar reflexes,

CADASIL

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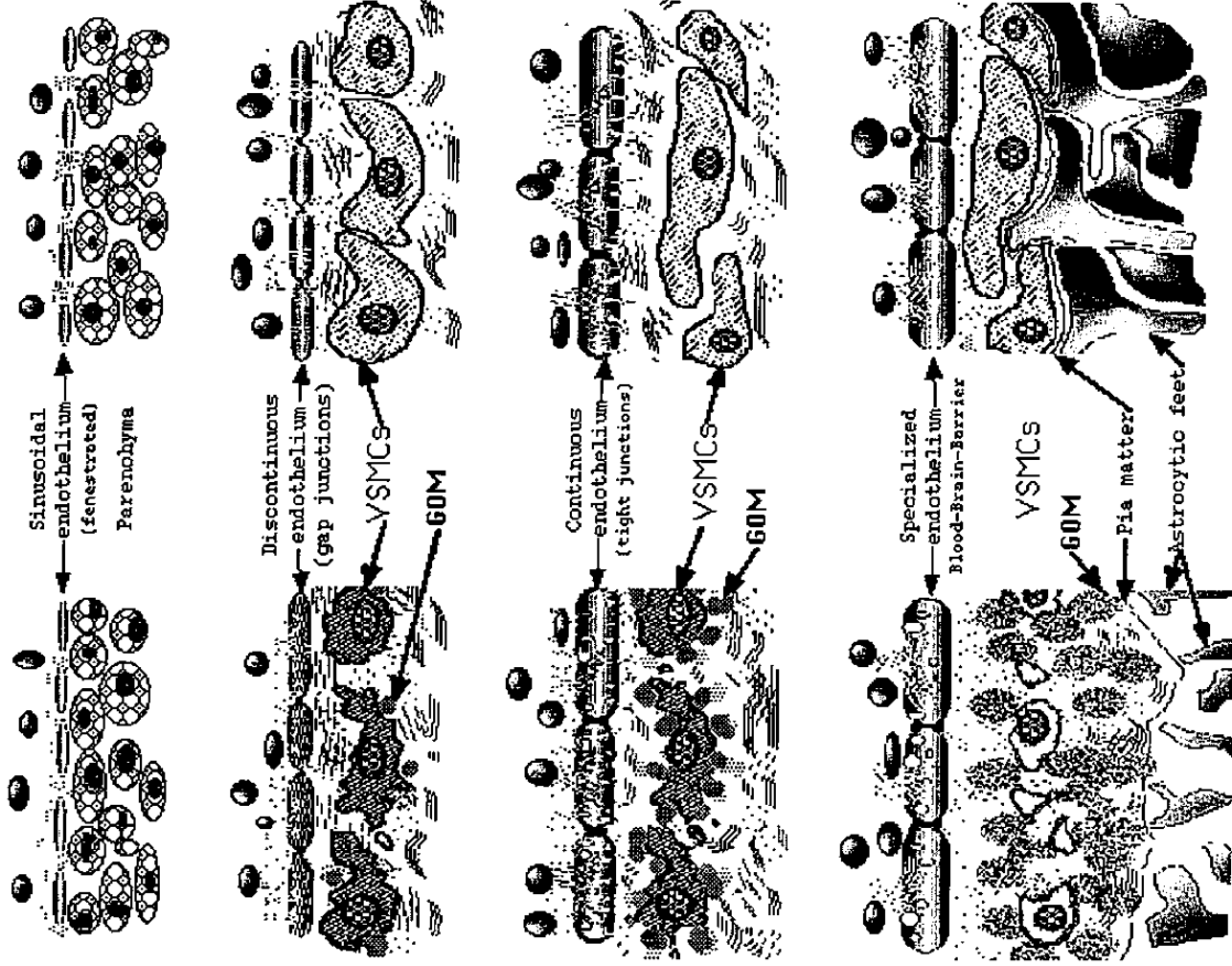


Fig. 7. Schematic representation of different CADASIL vessel walls compared with the corresponding normal vessel walls. Such a diagram is provided as a means of visualizing differences between vessel walls relying to either sinusoidal endothelium, discontinuous, continuous or particularly blood-brain barrier endothelium. These differences may relate the brain involvement to the dramatic modifications observed in the brain vessel walls.

and primitive reflexes are the most common neurological abnormalities associated with leukoaraiosis, and their existence is thought to be related to damage to the subcortical brain regions. This is puzzling, because the significance of this leukoaraiosis is not yet understood due to still-inadequate pathological correlation and because it is

now evident that such lesions are also observed in clinically normal individuals and can be identified in 22% of persons under the age of 40 (53, 58). Consequently, the simple presence of leukoaraiosis within an inherited condition might allow us to pick out some individuals suspected of belonging to a CADASIL family when other

causes of small-vessel disease have been discounted. Nevertheless, two opposing situations may occur and need to be clarified. Firstly, some asymptomatic patients or young patients may have an inconclusive result in MRI as reported by Joutel (19). In the case cited, skin biopsy and genetic analysis gave positive information. Secondly, given that similar clinical and neuroimaging findings can be observed in other vascular leukoaraioses, it is possible to overinterpret its significance in affected subjects. So in a large family (59), two first relatives presenting with similar findings were not found to carry the same haplotype in the light of genetic analysis as confirmed by skin biopsy results. The first presented characteristic vessel wall GOM deposits; the second showed abnormally thin vessel walls without GOM, suggesting a BSAE of unknown origin. Both these points raised the problem of the accuracy of neuroimaging in diagnosis and the necessity of completing the investigations with a test for CADASIL gene mutation or a skin biopsy before providing genetic counseling. Finally, a skin biopsy may lose its sensitivity in patients under age 30; thus, direct DNA testing for gene mutation will now be the major tool for making a differential diagnosis. Young patients presenting a BSAE in the absence of chronic arterial hypertension (60, 61), the 20% of BSAE patients that did not suffer from chronic arterial hypertension (62), and patients presenting "vascular glycosaminoglycans with periventricular leukoencephalopathy" (63) might be identified as having CADASIL or be ruled out. On the other hand, several hereditary conditions may be misdiagnosed, such as the "familial young-onset arteriosclerotic leukoencephalopathy" reported in Japanese pedigrees, which is an autosomal recessive condition associated with alopecia and skeletal abnormalities and a systemic arteriosclerohyalinosis (64–67). Another example of misdiagnosis could be the hereditary leukoencephalopathy recently reported by Lossos et al (68), a disorder with increased skin collagen content presenting a progressive dementia associated with palmoplantar keratoderma. Last of all, multiple sclerosis can be difficult to differentiate from CADASIL, particularly at onset.

New Outlook

In the last 4 decades, significant progress has been made towards a more comprehensive understanding of cerebrovascular diseases. New therapeutic methods have been discovered in the fields of hypertension and coronary heart diseases. New peripheral investigations have identified a variety of conditions leading to leukoaraiosis. In spite of this progress, many conditions benefiting from extensive and very informative clinical and neuroimaging studies remain outside the area of fundamental research. In fact, pathological investigations have been limited and often reflect a completed disease process. With the description and genetic identification of CADASIL, a new

avenue has been opened in the cerebrovascular field; this was recognized by Bowler and Hatchiski (69) in 1994, who said that "the significance of the findings goes well beyond the condition itself." Now, the discovery of *Notch 3* gene mutations in CADASIL is a new crucial step forward for further research (19). First, sporadic patients and new families could either be included or ruled out and new, adult-onset conditions causing dementia might be identified. Second, genotype/phenotype correlation studies could help to establish the function of the protein Notch, which corresponds to a transmembrane receptor, probably with different functional domains (70). Third, the identification of the different mutations may open the way for research using animal models. Furthermore, since a genetically inherited type of migraine with no leukoaraiosis also maps to the same locus on chromosome 19 (71) as well as the hereditary paroxysmal ataxia (72), gene identification will allow us to determine if these 3 conditions are allelic disorders and are likely to be new candidates for ion-channel diseases with differing phenotypes.

Since CADASIL is a systemic vascular disease, peripheral investigations should be considered. As in hypertension or other systemic vascular diseases, the basic research and therapeutic trials could easily be verified either in human or animal models. In the last 4 years, in an attempt to identify the CADASIL patients, the systematic in-depth examination of the skin vessel walls has allowed us to observe the presence of several modifications either in endothelial cells or VSMCs or in the extracellular matrix in several subcortical dementia conditions. These findings pave the way for research into pathophysiology, and more collaborative studies are needed to verify the accuracy of some of the findings before genetic linkage is performed. They make it possible to study some neurodegenerative diseases with diagnostic criteria that were previously dependent solely on confirmation at necropsy. So, all of this morphological information seems to have far-reaching consequences. Moreover, once a neurodegenerative disease is related to a systemic vascular disease, it becomes easier to research. Consequently, therapeutic research can then be applied and pursued further.

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