

## CASE REPORT

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## Small arterial granular degeneration in familial Binswanger's syndrome

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**Abstract** A 55-year-old mildly hypertensive woman died after having developed a subcortical dementia during the past 9 years, with focal neurological signs. She presented at the age of 46 years with short episodes of dizziness and diplopia, suggesting that transient ischemic attacks involved the posterior fossa structures. Over the next 8 years, she developed difficulty in walking, urinary incontinence and seizures. On examination in 1989, she was severely demented. There was tetraparesis, bilateral arm and leg spasticity with hyperreflexia and bilateral Babinski signs. She showed epilepsy partialis continua involving the eyes, left hemiface and limbs. CT showed hypodensity of the white matter and lacunes in the basal ganglia and centrum semiovale, moderate hydrocephalus with cerebellar and cortical atrophy.

Clinical and radiological features were similar to those of Binswanger's disease. Similar cases had occurred in the family affecting the patient's grandfather, father and two brothers, suggesting an autosomal dominant hereditary disease.

Postmortem examination disclosed a Binswanger type of leukoencephalopathy caused by a peculiar microangiopathy characterized by a slightly basophilic small arterial granular degeneration of the medial sheath associated with the presence of ballooned smooth muscle cells with clear cytoplasm. Electron microscopic study revealed degenerative changes in the parietal vessels with notable increase of basal-membrane-type material and electron-dense granular deposits. These lesions could correspond to a specific familial pathology of the small arteries of the brain. They are identical to those reported in some patients

with autosomal dominant inheritance. For other patients with similar clinical features and the same familial pattern, reported as "hereditary multi-infarct dementia" and "chronic familial vascular encephalopathy", there are no sufficient objective pathological facts to consider that they have the same disease. The absence of amyloid pathology in our case differentiates it from the hereditary central nervous system amyloid angiopathies. Finally, patients with non-familial Binswanger's syndrome, but without hypertension, could exceptionally have the same vascular granular degeneration. Presumably, this vasculopathy of uncertain pathogenesis could be related to a metabolic disorder of the basement membrane of smooth muscle cells.

**Key words** Binswanger's syndrome · Cerebral arteriolosclerosis · Leukoaraiosis · Dementia

In 1894 Binswanger [4] proposed the term "encephalitis subcorticalis chronica progressiva" to refer to a non-inflammatory white matter disease, whose clinical course was characterized by a slowly progressive intellectual deterioration starting in the fifth-sixth decade, with seizures and stroke-like events, but the most frequent nomination has been "subcortical arteriosclerotic encephalopathy" (SAE). Numerous articles have described the clinical, radiological and pathological features including the light microscopic vascular pathology but without providing ultrastructural aspects of the vessels [1, 7, 8, 10–12, 16, 18, 21, 23, 27, 33].

A diagnosis of SAE has been based mainly on neuro-radiological data, with the presence of multiple subcortical lacunes, periventricular white matter changes, central atrophy, and secondary hydrocephalus, on computed tomography (CT) and/or magnetic resonance imaging (MRI) [12, 18, 24].

In a recent comprehensive article, a scheme for the diagnosis of this entity has been advanced [3]. This is mainly based on clinical features, but there is still a

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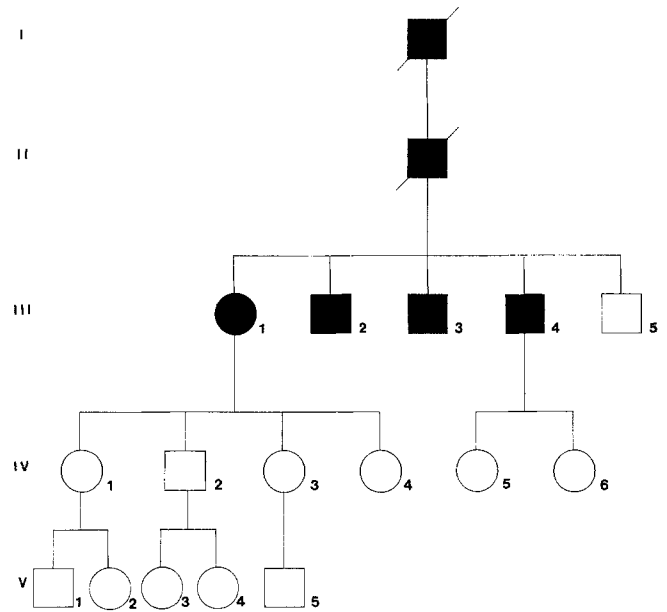
need for other diagnosis criteria. Some of them include dementia, vascular risk factors such as hypertension, diabetes, myocardial infarction, cardiac arrhythmia or congestive heart failure, acute strokes with or without recovery and evidence of cerebral subcortical dysfunction. The neuropathological aspects of the parenchymatous brain lesion are relatively constant with a subcortical topographic expression. However, the vascular pathological substrate is heterogeneous. Binswanger [4] only referred a severe atheromatous macroscopic aspect of the arteries of the brain, not showing histological examination.

In a great number of patients the basic pathology is that of a small arteriosclerosis and arteriolosclerosis; nevertheless, there are many cases, some of them with an inherited pattern, also included under this eponym, in spite of the presence of different histopathological vascular lesions [2, 6, 9, 22, 26, 28, 30–32].

We report the neuropathological study by light and electron microscopy of a patient with familial vascular dementia and topographic lesions characteristic of Binswanger's syndrome but with unusual vasculopathic lesions.

## Materials and methods

A 55-year-old woman was admitted to the hospital in November 1989 because of focal motor status epilepticus. The patient was healthy until 9 years before when she started to present short episodes of dizziness and diplopia, suggesting transient ischemic attacks involving the posterior fossa structures. In an angiographic study, unilateral hypoplasia of the right vertebral artery was found. Later she presented psychiatric symptoms (depression, apathy, ...). Over the following 8–9 years she suffered impairment of different spheres of mental activity (memory, cognition, emotion, alterations of mood and behaviour, ...) as well as sleep disturbances and confusional states. She attempted to commit suicide on several occasions. There was no prominent aphasia, agnosia or apraxia. This clinical picture was progressive, worsening after an ictus (usually transient ischemic attacks) involving different arterial territories. During that time, she also developed difficulty in walking, urinary incontinence and secondarily generalized seizures. She had mild hypertension, without other risk factors for cerebrovascular disease such as cardiac disease, diabetes, hyperlipidemias or peripheral arteriopathy. On examination in 1987, she showed a severely impaired mental state, with signs of focal involvement such as mild pyramidal quadriplegia, bilateral arm and leg spasticity with hyperreflexia, ankle clonus and bilateral Babinski signs. She also presented a pseudobulbar syndrome, a small-stepped wide based gait, slight incoordination in finger-to-nose and heel-to-shin testing, and urgency of micturition. Funduscopic examination was normal as well as Chest X-ray and Electrocardiogram. Laboratory data for blood and urine studies were normal, including electrolytes, calcium, urea, liver function tests, vitamin B12, folate, sedimentation rate, VDRL, human immunodeficiency virus antibody, thyroid function tests, plasma pyruvate and lactate, porphyria screening, cortisol levels with ACTH stimulation, urinary and plasma amino acids, copper studies, antinuclear factor and other immunological studies. The estimation of Cystatin C in the CFS was not investigated. The electroencephalogram showed generalized slowing with pronounced delta waves and epileptic spikes in the left parietotemporal regions. A CT of the cranium showed moderate dilatation of the lateral and third ventricles, cortical atrophy, mild cerebellar atrophy and hypodensity of the deep white matter and lacunes in the basal ganglia and centrum ovale.



**Fig. 1** Family pedigree. Filled symbols, symptomatic subjects; empty symbols, healthy individuals; oblique slash, deceased; squares, male subjects; circles, female subjects

At the age of 55 years, when she was admitted into our hospital, the patient's status had clearly deteriorated approaching a state of akinetic mutism. In the last 2 weeks of her life she became more obtunded and died after 1 week of a deepening coma from a generalized decubitus infection, 9 years after the onset of the disease and 6 months after entering our hospital. Autopsy was performed a few hours later.

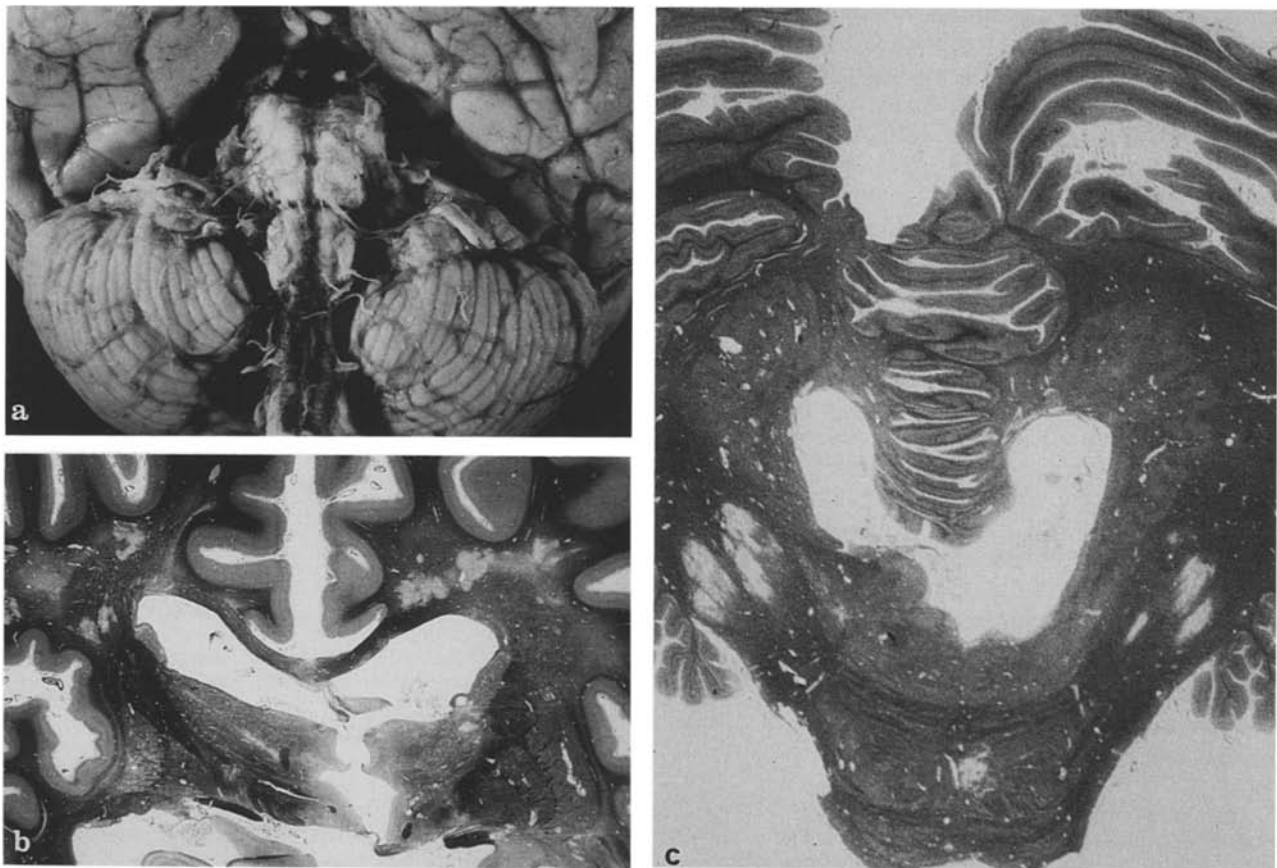
Grandfather and father were deceased, affected by an apparently similar entity. Sixteen members of her family underwent clinical investigation (Fig. 1). The 16 subjects examined belonged to generations III (5 subjects), IV (6 subjects) and V (5 subjects). Three (propositus and 2 male siblings) belonging to generation III had suffered episodic headache, suggestive of migraine and stroke-like episodes, which started between 40 and 50 years of age. Also two of them developed subcortical dementia. Another sibling showed psychiatric disturbances.

## Morphopathological methods

The brain was fixed in 10 % formalin for 2 weeks and selected tissues were several hours postfixated in Bouin and embedded in paraffin. In addition, entire coronal slices of the cerebrum were taken. Sections, 4  $\mu$ m thick, from the small samples were stained using HE, periodic acid-Schiff, Masson's trichrome, Congo red, Elastica van Gieson, Orcein and von Kossa's stain. A tissue block of brain stem was stained with Alcian blue H8GX as a 0.1 % solution in 0.05 M acetate buffer (pH 5.7) with sufficient  $MgCl_2$  to give concentrations of 0.2 M and 0.8 M.

Immunohistochemical stains of the affected blood vessels were performed on paraffin sections using antibodies against IgG, IgA, IgM, kappa and lambda chains, actin, factor VIII, laminin and collagen type IV.

Samples for electron microscopy were obtained from an anterior spinal artery, fixed in 10 % formalin, washed in cacodylate buffer and embedded in epoxy resin.



**Fig. 2** a Base of the brain. Pons mild atrophy with depressed anterior surface and absence of important atheromatous changes. b, c Moderate ventricular dilatation and microinfarcts in centrum semiovale, pons and middle cerebellar peduncles. Loyez stain

#### Neuropathological findings

##### *Macroscopic examination*

Macroscopic examination of the 1010-g brain showed narrowing of the *giri* and widening of the sulci in the fronto-parietal lobes and irregular atrophy of the anterior part of the pons. The circle of Willis showed patchy and mild atheromatous changes (Fig. 2a). Coronal sections through the cerebral hemispheres and transverse sections through the brain stem showed a symmetrical dilatation of the lateral, 3rd and 4th ventricles.

Loyez-stained coronal sections revealed several small microinfarcts in the centrum semiovale, internal capsule, spinal cord and brain stem, especially in the pons and middle cerebellar peduncle (Fig. 2b, c). Some ill-defined zones of discoloration were present in the periventricular white matter, extending from the frontal to the occipital lobes, corresponding to variable degrees of demyelination.

##### *Microscopic changes*

Microscopic changes were those of infarcts in different stages, with areas of myelin loss, macrophage reactions, cavitation and fibrillary gliosis. A wide variety of vascular changes, dependent on the stage of the lesions, were present in the meningeal and intraparenchymatous vessels, mainly in the small arteries and arterioles of the pons (Fig. 3a) and basal ganglia. Cortical vessels were usually better preserved.

A granular deposit of slightly basophilic material in the medial sheath was the most prominent finding in the initial stage (Fig. 3d, e); these lesions did not correspond to a calcifying angiopathy. The granularity was consistently positive with periodic acid-Schiff and Alcian blue at 0.2 M and lower concentrations of  $MgCl_2$ . Characteristically, it was elastophilic with Elastica van Gieson stain but not orceinophilic. The material was negative with von Kossa and Congo red stains. Later, decreasing and disappearance of the smooth-muscle cells and fibrosis of the media were observed but single and scattered ballooned smooth muscle cells with clear cytoplasm could be seen, some of them binucleated (Fig. 3d). The perivascular spaces occasionally contained a mild macrophage infiltration loaded with hemosiderin; but generally there was a sparse perivascular space, almost totally occluded by connective tissue and the parenchyma surrounding the vessels showed gliosis.

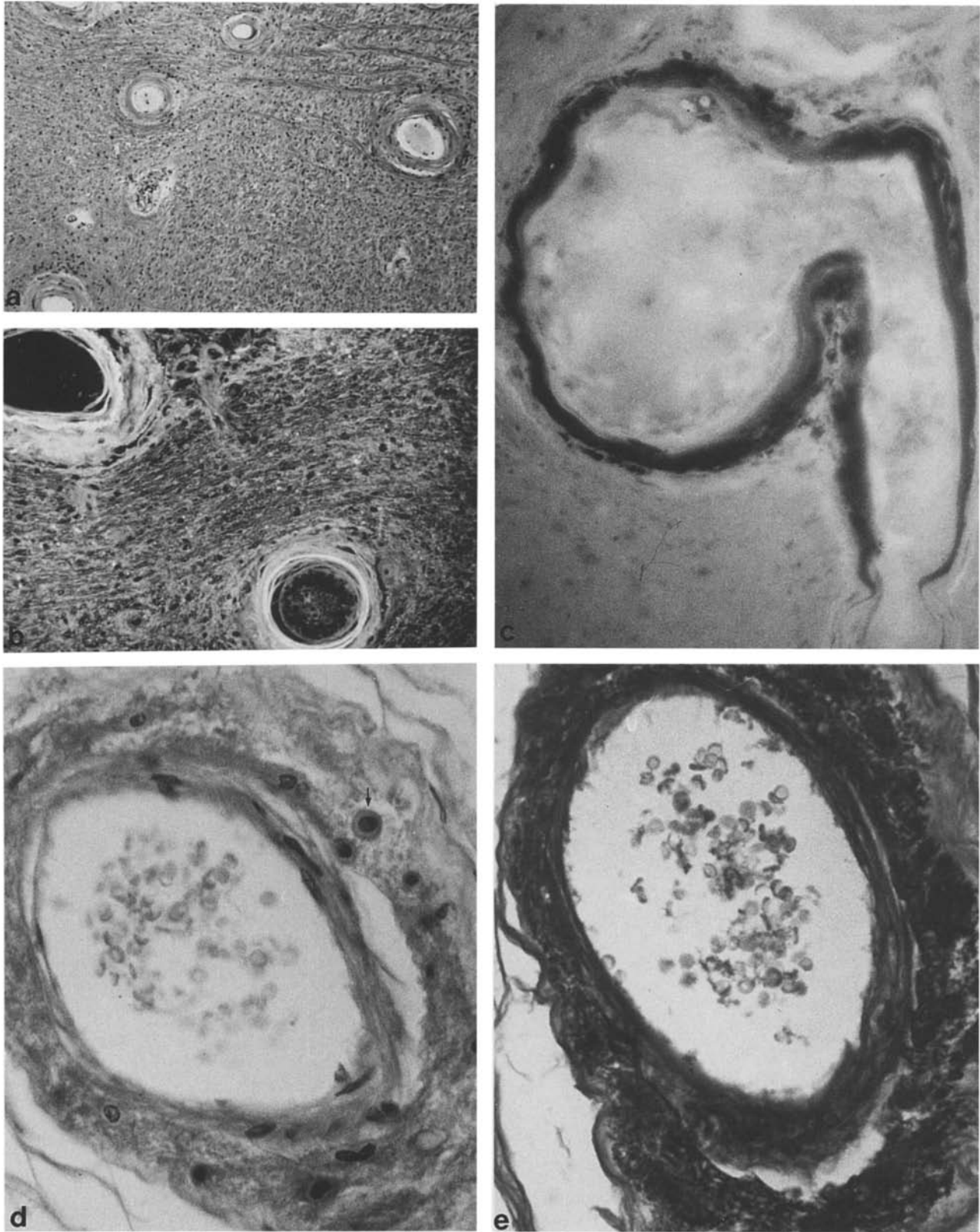
Other lesions that could be observed were: Charcot's microaneurysms, lipohyalinosis of the arteriolar walls (Fig. 3c) and severe narrowing of the lumina of some vessels. Reduplication of the internal elastic lamina was rarely seen in the small arteries (Fig. 3b).

The immunohistochemical reactions showed an absence of deposition of IgA, IgG, IgM, kappa and lambda chains in the arterial walls. However, the intensity for type IV collagen was very strong. The results with laminin were undefined. Many ballooned smooth muscle cells were not labelled with actin.

The histological examination of striated muscle and sural nerve did not show any specific pathological changes.

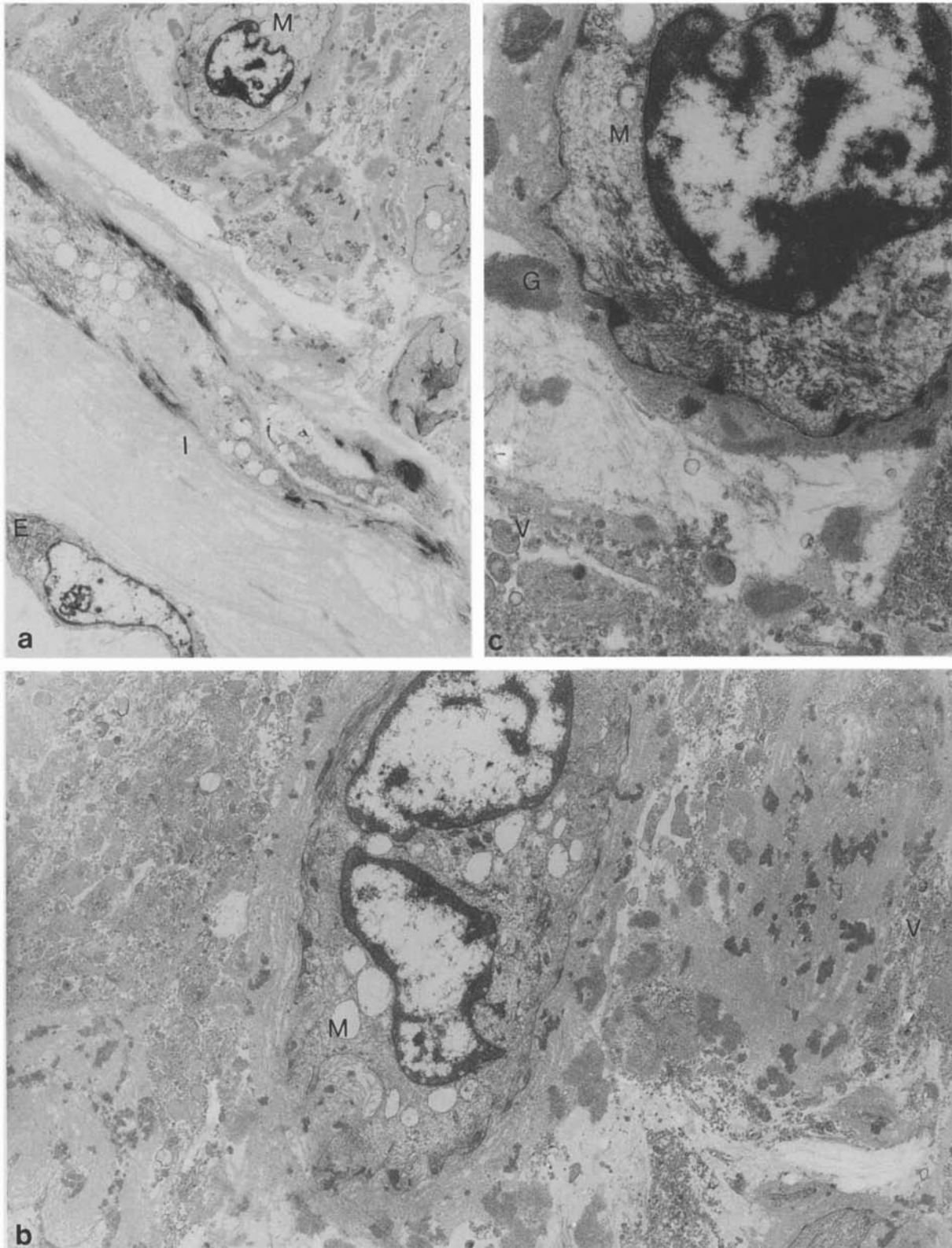
##### *Electron microscopic study*

Electron microscopy of a spinal artery was characterized by the presence of a great amount of basement-membrane deposits and granular and electron-dense material with degenerative lesions of muscle cells (Fig. 4a-c).



**Fig. 3** **a** Small pons arteries and arterioles showing arteriosclerosis and arteriosclerosis changes. HE,  $\times 60$ . **b** No replication of internal elastic lamina in small arteries. Ultraviolet lamp-excited HE,  $\times 160$ . **c** Lipohyalinosis; Oil-Red-O  $\times 200$ . **d** Granular degeneration

of the media in a small artery with single and scattered ballooned smooth muscle cells. HE,  $\times 375$ . **e** Elastophilic aspects of granular degeneration. Elastica Van Gieson stain,  $\times 375$



**Fig. 4 a** Electron microscopic appearance of a spinal artery with degenerative changes in the medial sheath.  $\times 3300$ . **b, c** Smooth muscle cell surrounded by basement membrane-like material,

granular electron-dense deposits and vesiculated structures. **b**  $\times 5900$ , **c**  $\times 13\ 220$ . *E*, Endothelial cell; *G*, granular electron-dense material; *I*, intima; *M*, muscle cell; *V*, vesiculated structures



### Systemic pathological findings

The heart was of normal weight (350 g). The wall of the left ventricle showed only a mild hypertrophy (13 mm). The four chambers, atrioventricular valve apparatus, semilunar valves and great vessels were normal. Aortic arch and the carotid system were unremarkable. The kidneys showed benign nephrosclerosis and ballooned muscle cells, but no granular degeneration, was appreciated in some arteries.

### Discussion

In Binswanger's disease (BD), atheromatosis is usually found involving both the extracranial arteries and the large vessels at the base of the brain [1, 4, 7, 10, 11, 21]. In addition to these atherosclerotic changes of the large vessels, the small arteries and arterioles of the cerebral white matter, basal ganglia and sometimes pons and cerebellum show thickening, fibrosis and some mural hyalinization with lipid deposit (lipohyalinosis). Because of the severe arteriolosclerotic lesions, the term subcortical arteriolosclerotic encephalopathy would seem as appropriate as the well-known subcortical arteriosclerotic encephalopathy (SAE).

In this patient, the evolution of the dementia was clearly in connection with acute neurological symptoms and/or CT findings, suggesting deep vascular lesions of the brain. Although the clinical and radiological features of our patient resemble those of patients with BD, important differences exist. Typically, patients with BD are elder and the presentation of the disease is sporadic. Our patient was middle-aged and she also had a positive family history, suggesting an autosomal dominant hereditary disease. On the other hand, the vascular pathological features in our patient, affecting small arteries and arterioles, were similar to classic BD but with an essentially distinctive feature, consisting of a granular degeneration of the medial sheath (small arterial granular degeneration, SAGRADE). This type of pathology is clearly different from amyloid angiopathy which affects some patients with BD [5].

There have been a few reports of disorders in the literature characterized by a slowly progressive familial dementia, stroke-like episodes and periventricular white matter changes resembling BD. In patients with autosomal dominant inheritance suffering from "familial subcortical dementia with arteriopathic leukoencephalopathy" [6], and "leukoencephalopathy with subcortical strokes" [2], the small arterial pathology was identical to our case. Microscopically the intima is generally normal, although isolated arteries can show fibrosis or elastosis and the internal elastic lamina frequently present thickening and reduplication or, sometimes, fragmentation. An artefactual dissection between intima and elastica can be occasionally observed. The basic lesion is a granular degeneration of the medial sheath that in our experience is slightly basophilic, PAS positive, alcianophilic and elastophilic with Elastica van Gieson's stain; however, it is not orceinophilic. In the

media, muscle cells degenerate and finally disappear, leaving the tissue with a collagenous sclerotic appearance. Some persisting cells show a globular aspect, carinomegaly and binucleation. Isolated vessels display a progressive thickening of the wall with severe narrowing of the lumen and others can suffer plasmatic insudation-lipohyalinosis or Charcot's microaneurysms. In our case, "état criblé" does not exist as it does in other reports; however, an adventitial fibrosis and perivascular gliosis was marked. This wide variety of vascular changes could depend on the stage of the lesions, although finally they are not different from the small arteriosclerosis and arteriolosclerosis that characterize classic BD, except for the SAGRADE which is the only essential pathological feature that could define the present case as a new disease. The coincidental familial occurrence in all these patients, exceptional in classic BD, favors the existence of a new autosomal dominant hereditary vasculopathy that could be diagnosed by indication of a leptomenigeal biopsy. The etiopathogenesis is not known but histochemical, immunohistochemical and electron microscopic results supports a disturbed metabolism of the muscle cell basement membrane. The common absence of hypertension (our patient was only very mildly hypertensive) suggests a new vasculopathy, although some pathological aspects are reminiscent of those of chronic hypertension where the medial sheath is described as irregularly atrophic with a paucity of muscle cells and with accumulation of cellular debris and basement material [29]. Furthermore, in muscle cells, mechanisms of endoreplication may result in a hypertrophic aspect [20] that could correspond to the caryomegalic cells seen in our patient. However, the pathological substrate of hypertension has never been manifested as a SAGRADE of the medial sheath.

In "hereditary multi-infarct dementia", Sourander [26] considered several individuals suffering from an unrecognized type of multi-infarct dementia, with an autosomal dominant transmission that was caused by an occlusive cerebrovascular disease, affecting particularly leptomenigeal and deep cerebral small arterial vessels regions. Although some authors consider it to the same entity [2, 6], from our point of view an objective uniformity with our arterial pathological findings does not exist. The absence of SAGRADE and the existence of intimal fibrinoid necrosis associated with mural infiltration with inflammatory cells in Sourander's description supports a different disease. In an other report on hereditary multi-infarct dementia there were no pathological studies [25].

In "chronic familial vascular encephalopathy" [28], the small arterial pathology could be similar, mainly in the distinctive appearance of muscle cells in which the nucleus is surrounded by a large vacuole occupying a great space of the cell. However, there is no description of granular degeneration in this disorder which has been considered similar to the hereditary multi-infarct dementia [26].

An autosomal dominant “familial cerebral amyloid angiopathy with non-neuritic amyloid plaque formation” has been described with onset around the fifth decade [22]. The clinical aspect includes a progressive dementia and occurring occasionally stroke-like episodes. The pathological features are characterized by a widespread amyloid angiopathy with a periventricular white matter change resembling Binswanger’s leukoencephalopathy. Although a pathogenetic relationship does not exist in our case (persistently negative with Congo red stain), we observed parietal vessel alcianophilia, attributed to glycosaminoglycan deposition, and other basement membrane-related abnormalities that could indicate an amyloidogenic situation [17]. However, the immunohistochemical determination of serum amyloid A and P components were also negative [2]. In other hereditary central nervous system amyloid angiopathies, neuropathological aspects of BD have not yet been reported [13–15].

Other patients with familial subcortical vascular encephalopathy are clinically characterized by alopecia, lumbago and the possible existence of an autosomal recessive transmission [31, 32]. We found no objective data in the pathology of these cases, to indicate that they were similar to our findings.

Another small group of sporadic BD encephalopathies with unconventional vascular pathology has been reported. In a patient with BD severe arteriolosclerosis was described in the absence of chronic arterial hypertension [19], but in some arterioles the affected media had undergone granular degeneration with loss of muscle nuclei, as with our patient. Future investigations on the vascular pathology of BD patients without hypertension may increase the incidence of these peculiar findings.

In a report on the “vascular glycosaminoglycans with periventricular leukoencephalopathy”, Torack [30] described a characteristic alcianophilia in the thickened cerebral arteries, but there was no mention of medial granular degeneration. Moreover, the leptomeningeal vessels appeared normal and small arteries and arterioles in hemispherical white matter frequently contained calcium. The parietal alcianophilia that was observed in our case could be similar to this, but the pattern of alcianophilia was different because Alcian blue only binds at concentrations of  $MgCl_2$  of 0.2 M or lower.

Finally, the “sclerosing vasculopathy of the central nervous system in nonelderly demented patients” [9] is a different disease. The pathological findings involve arterioles, venules and capillaries, without SAGRADE. However, there were some similarities in the electron microscopic findings. The overall impression was that of a disorganized medial layer with mature collagen mixed with fragments of elastin, basement membrane and granular electron-dense extracellular material. The presence of cells containing complex lysosomes in the vascular wall also represents a difference with our case.

In conclusion, the vascular pathology in BD consists of arteriosclerosis and arteriolosclerosis but other types of pathology can indicate the same subcortical affection (Binswanger’s syndrome). One of these is the SAGRADE of the medial sheath in cerebromeningeal vessels, which constitutes the specific pathology of a new recently described autosomal dominant disease, which can be diagnosed in a leptomeningeal biopsy.

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