

Case Report

Autosomal Dominant Leukoencephalopathy and Subcortical Ischemic Stroke

A Clinicopathological Study

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Background and Purpose: We recently described an autosomal dominant syndrome characterized mainly by recurrent strokes and neuroimaging evidence of leukoencephalopathy. We now report the pathological findings in one of the affected subjects.

Case Description: A 40-year-old woman experienced her first grand mal seizure in 1971. From 1983 on she suffered recurrent strokes, seizures, and psychiatric disturbances with depressions, manic episodes, and dementia. In 1988, after her fourth stroke, she became tetraplegic with a severe pseudobulbar palsy, and she died in 1990.

Pathological examination disclosed a recent capsulolenticular hematoma, multiple small deep infarcts, a diffuse myelin loss and pallor of the hemispheric white matter, and a widespread vasculopathy of the small arteries penetrating the white matter. The arterial wall was markedly thickened with an extensive nonamyloid eosinophilic deposit in the media and reduplication of the internal elastic lamella.

Conclusions: The underlying lesion of this hereditary disorder is located in the small arteries and is of unknown etiology. It differs from arteriosclerotic and amyloid angiopathies but is similar to that described in some cases of hereditary multi-infarct dementia. (*Stroke* 1993;24:122–125)

KEY WORDS • genetics • lacunar infarction • leukoencephalopathy

We recently reported the prospective survey of a French family presenting an autosomal dominant syndrome with strokelike episodes and leukoencephalopathy.¹ Of the 45 family members studied, nine had transient ischemic attacks and minor or major strokes with neuroimaging evidence of small deep infarcts and a widespread white matter disorder. Eight other family members were clinically normal but had identical neuroimaging signs of leukoencephalopathy.

We now report the pathological findings in one of the nine clinically affected subjects.

Case Report

This previously healthy woman (family member III-19 in Reference 1) was 40 years old in 1971, when she first experienced a grand mal seizure. She was well until 1983 when she suffered two other grand mal seizures,

which prompted treatment with phenobarbital. In November 1983 she suddenly experienced numbness of the right hand and, 48 hours later, a right-sided weakness and dysarthria. She partially recovered, but she became apathetic and depressed a year later. She was treated with clomipramine and gradually improved. During succeeding years she had several grand mal seizures, frequent psychiatric disturbances with recurrent depressions, and a manic episode in 1985. Her neuropsychiatric status worsened in 1986 with an inability to perform usual daily activities, difficulties in walking, and occasional urinary incontinence. She was first examined in October 1986. She was dysarthric, jovial, logorrheic, easily distractible, and moderately demented. She was unable to walk and had a right-sided hemiparesis. She moderately improved, but in December 1986 she experienced several transient episodes of left face and arm tingling, followed by a permanent left-sided numbness. She remained stable until August 1988, when she suddenly developed a left hemiparesis with hemianopia. She did not recover, and in October 1988 she presented with a massive right-sided hemiplegia followed by status epilepticus; she was then tetraplegic with a severe pseudobulbar palsy. She did not improve and remained bedridden for the next 2 years. In December 1990 she suddenly became comatose and died a few hours later, at age 59. Brain neuroimaging (computed tomography and magnetic resonance imaging) showed diffuse white matter abnormalities (leukoaraiosis) together with small, deep, and well-delineated areas of hypodensity or abnormal signal.¹ Biopsy obtained from the left deltoid

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showed an accumulation of sudanophilic lipids within muscle fibers but no detectable abnormalities in the morphology and number of mitochondria.¹ Analyses of mitochondrial functions and mitochondrial DNA were normal in muscle cells as well as in peripheral mononuclear blood cells. Numerous laboratory and cardiovascular investigations (detailed in Reference 1) were essentially normal.

Postmortem Findings

Materials and Methods

Autopsy was performed 6 hours after death. The brain was examined after it was fixed in 10% formalin and embedded in paraffin and celloidin. Paraffin sections were stained with hematoxylin and eosin, reticulin, von Kossa's stain, Masson trichrome, periodic acid-Schiff, thioflavine-S, Congo red, Bodian silver impregnation combined with luxol fast blue, and orcein. Loyez stain for myelin was performed on celloidin sections. Frozen sections were examined by direct immunofluorescence using antibodies directed against immunoglobulin (Ig) G, IgA, IgM, IgE, κ and λ chains, C3c, and C1q (Behring). Immunohistochemical examination used peroxidase anti-peroxidase technique with monoclonal antibodies against actin (Sigma), desmin (Dako), vimentin (Amersham), serum amyloid A and P components (Dako), and CD68 for macrophages (Dako). Positive and negative controls were performed for immunofluorescence and immunohistochemical techniques.

Samples for electron microscopy were directly fixed in 2.5% buffered glutaraldehyde, postfixed in 1% osmium tetroxide, and embedded in epoxy resin. Semithin sections were stained with toluidine blue, and ultrathin sections were stained with uranyl acetate-lead citrate. Wavelength dispersive electron microscopy (Camebax; Cameca, Courbevoie, France) was also performed on ultrathin sections. Conventional and immunohistological techniques and electron microscopy were performed on visceral organs.

Results

The brain weighed 1,380 g. Gross examination showed a massive recent hematoma in the left cerebral hemisphere involving the caudate nucleus, internal capsule, lenticular nucleus, and thalamus, which had ruptured into the lateral ventricles; the white matter was grayish, with multiple small cystic lesions involving primarily the periventricular regions and the frontoparietal lobes. Numerous other cystic lesions affected the basal ganglia, thalamus, pons, and left nucleus dentatus. Basal arteries showed patchy atheroma without stenosis or occlusion. Examination of sections stained for myelin showed a diffuse white matter pallor with some preservation of the U fibers, predominantly in the frontal regions (Figure 1). In addition, small necrotic foci were scattered throughout the white matter, showing all degrees of destruction from a spongy looseness of the tissue with loss of myelin sheath to typical small (3–6 mm) cystic infarcts. Cortical gray matter and cortical arteries were normal.

Marked changes were observed in small arteries (100–400 μm) of the white matter, basal ganglia, thalamus, mesencephalon, pons, and cerebellum, and in the leptomeningeal arteries (500 μm). The most frequent

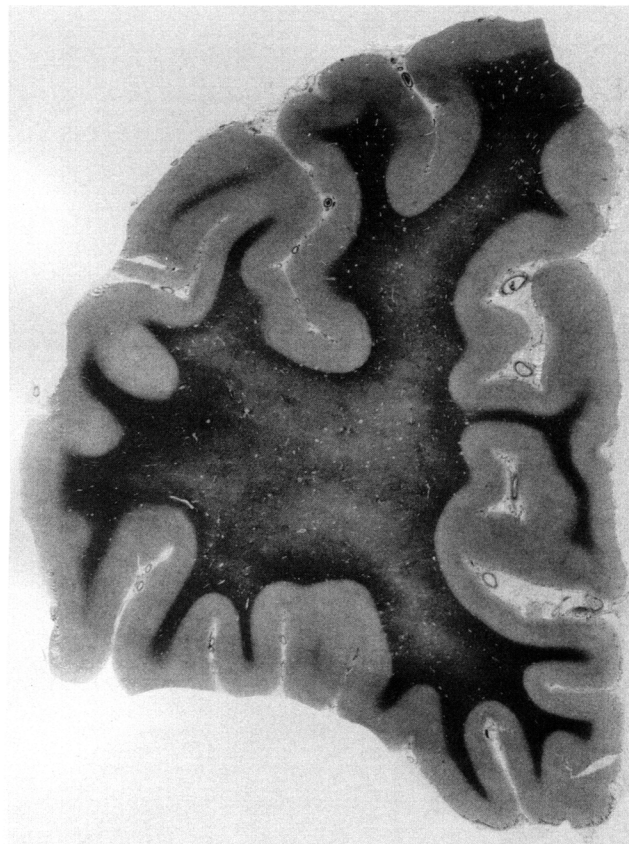


FIGURE 1. Diffuse myelin loss and pallor sparing the U fibers in the frontal white matter. Loyez stain, $\times 0.75$.

and striking lesion was a concentric thickening of the arterial wall, mainly due to a granular eosinophilic deposit in the media (Figure 2, upper panel). The deposit contained a few globular cells. Other lesions included hyaline degeneration of the media and reduplication and sometimes fragmentation of the internal elastic lamella (Figure 2, lower panel). No occlusion or thrombus was observed. The endothelium was intact. Dilatation of perivascular spaces with mild lymphocytic infiltration, iron pigment deposits, and astrocytic gliosis was frequent. Congo red, von Kossa's stain, and orcein were negative in the deposit, whereas periodic acid-Schiff was weakly positive. Immunofluorescence was positive with anti-C3c and -C1q antibodies in the media but was negative with the other antibodies. Immunohistochemistry for actin, desmin, vimentin, CD68, and serum amyloid A and P components was negative in the deposit. Stains for actin and desmin were positive in the globular cells, suggesting a myocytic origin.

On electron microscopic examination, the endothelial cells and basal lamina of the arteries and arterioles of the white matter were normal, whereas the media was markedly thickened by a deposit containing collagen, a few elastic fragments, and a granular electron-dense extracellular material (Figure 3). This material was located in the internal part of the media, reaching the basal lamina. No amyloid or intermediate filaments were visualized. Wavelength dispersive electron microscopy showed that the extracellular granular electron-dense material was not specific for mineral or metallic elements.

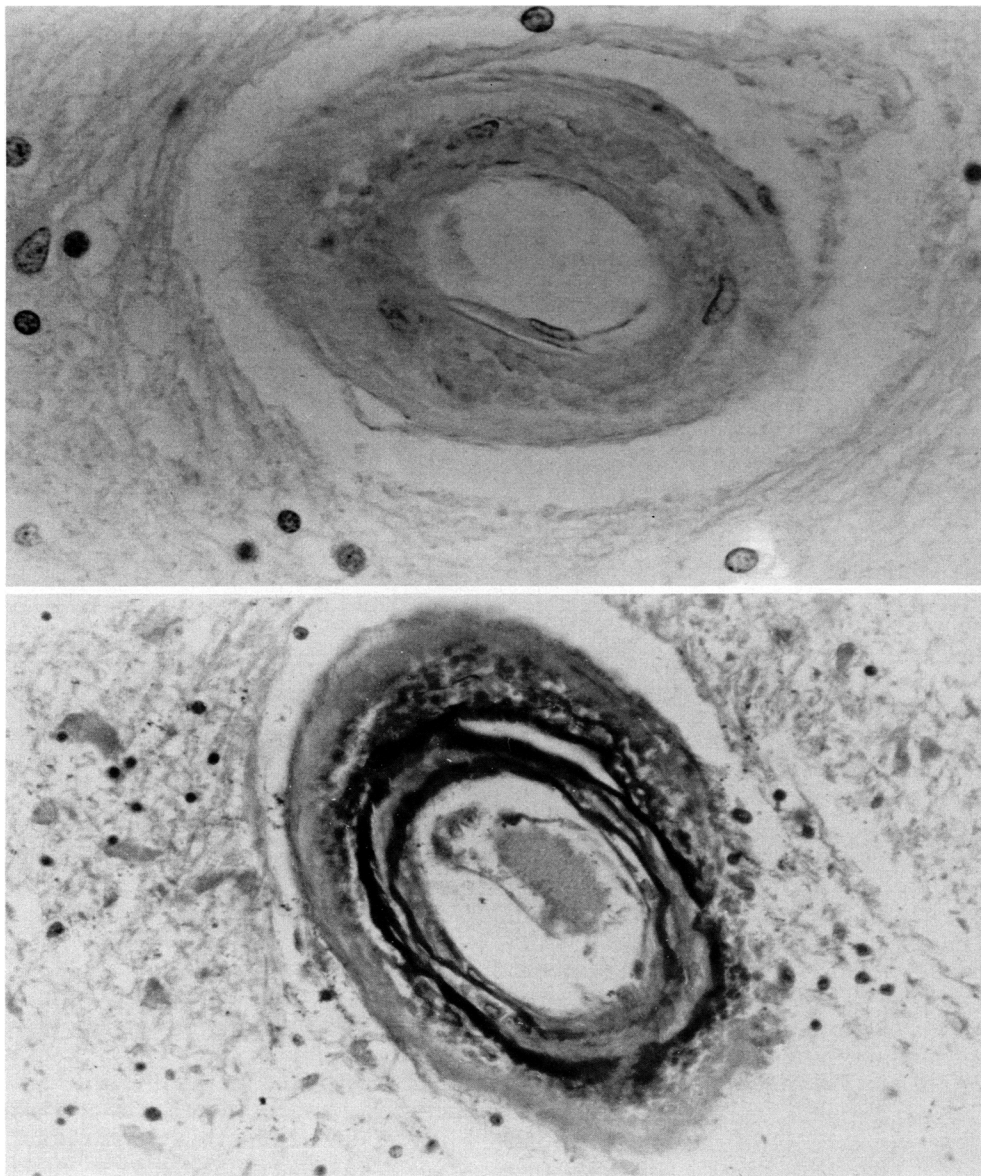


FIGURE 2. *Vascular changes in small arteries of the white matter. Upper panel: Granular eosinophilic material in the media. Hematein eosin stain, $\times 284$. Lower panel: Thickening and reduplication of the internal elastic lamella. Orcein stain, $\times 284$.*

Sections from the spleen, pancreas, heart, and kidneys showed only minor vascular changes with reduplication of internal elastic laminae in medium-sized arteries. Eosinophilic thickening of the media was seen in one small myocardial artery.

Discussion

The pathological data of this case are characterized by a large, recent capsulolenticular hematoma, multiple old small deep infarcts, a diffuse myelin loss and pallor of the hemispheric white matter, and widespread vascular changes primarily involving the small arteries penetrating the white matter. The most striking feature of this vasculopathy was a concentric thickening of the arterial wall with an extensive granular eosinophilic deposit in the media and a reduplication of the internal elastic lamella. Similar lesions were observed in leptomeningeal arteries and very rarely in visceral organs. The nature of the granular deposit in the media is unknown. The histological aspect is not that of fibrinoid necrosis. Stains for amyloid were negative, and no

amyloid or intermediate filaments were visualized by electron microscopy. Direct immunofluorescence studies were negative except for C3c and C1q, a finding of low specificity in vessels with hyaline degeneration.²

The clinical, neuroimaging, and neuropathological presentation of this case, with its association of multiple small deep infarcts and leukoencephalopathy, is suggestive of Binswanger's disease.³ However, the present disorder differs from this condition by its earlier onset, the low rate of hypertension, the absence of large-artery disease, the presence of a deposit in the media of small penetrating arteries, and the autosomal dominant pattern of inheritance. The present disease, with a terminal cerebral hemorrhage, could be reminiscent of hereditary cerebral hemorrhage with amyloidosis-Dutch type,⁴ but the absence of amyloid staining of the arterial deposit rules out this condition. Recurrent strokes, white matter disease, and muscular lipidosis are features of MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes) syndrome.⁵ However, the present condition

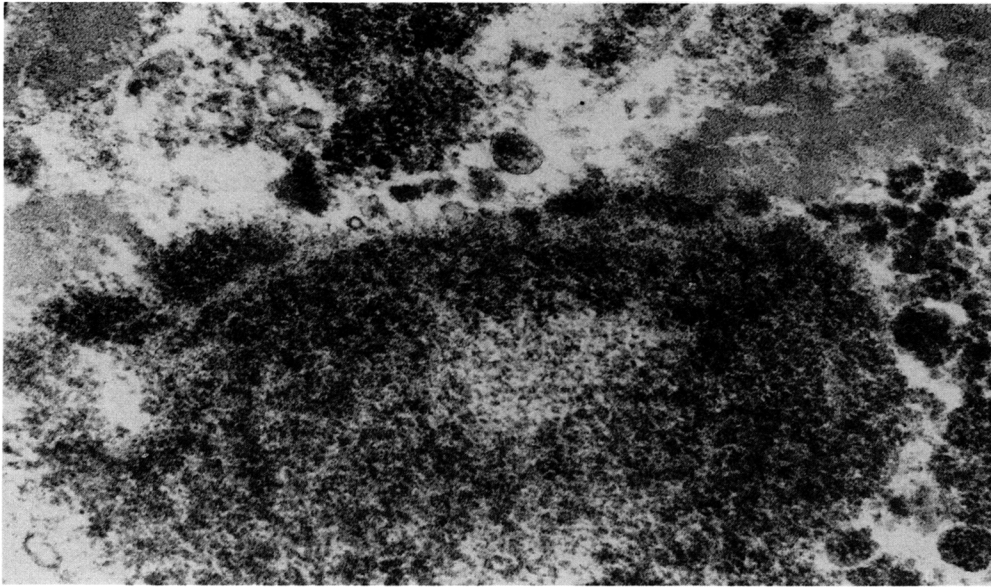


FIGURE 3. High-magnification electron micrograph of granular osmiophilic deposit in the media. Double stain with uranyl acetate-lead citrate, $\times 44,730$.

clearly differs in its later onset, clinicopathological features, and absence of functional and DNA mitochondrial abnormalities.

Four other families⁶⁻⁹ have been reported with autosomal dominant recurrent strokes, leukoencephalopathy, and pathological data sharing numerous similarities with those observed in our patients. Cases of multi-infarct dementia reported by Sourander and Walinder⁶ and Davous and Fallet-Bianco⁷ are identical to ours, with the same clinical and neuroimaging pattern,⁷ the same leukoencephalopathy with multiple small deep infarcts, and the same underlying small-vessel nonarteriosclerotic disorder with a nonamyloid granular deposit in the media. The family reported by Sonninen and Savontaus⁸ is in all respects similar, but the absence of microscopic examination of the brain does not allow characterization of the underlying arteriopathy. The family described by Stevens et al⁹ is again remarkably similar, except for the presence of proliferation of the intima with occasional occlusion of small deep arteries.

Thus, in these five families, there appears to be a new autosomal dominant condition characterized clinically by recurrent strokes and dementia in the absence of hypertension, macroscopically by multiple small deep infarcts and leukoencephalopathy, and microscopically by a small-artery disease different from arteriosclerotic and amyloid angiopathies. A very similar condition has been reported in nonfamilial cases^{10,11} and in two Japanese brothers belonging to a family with a high degree of consanguinity.^{12,13} Other families with subcortical ischemic strokes, dementia, and leukoencephalopathy have been reported, but without pathological data.^{14,15}

The striking similarity of all the above mentioned cases suggests the same underlying condition, which might be much more frequent than presently estimated. However, this cannot be firmly established until the cause of the present disease and its underlying genetic defect are elucidated.

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