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Familial Arteriopathic Leukoencephalopathy: Imaging and Neuropathologic Findings

Peter Glusker, Dikran S. Horoupian, and Barton Lane

Summary: We present the clinical, imaging, and neuropathologic data for a family with an autosomal dominant, nonhypertensive, progressive cerebral arteriopathy and leukoencephalopathy. Clinical presentation was characterized by progressive dementia, gait abnormalities, and, in some, Parkinson-like symptoms. MR abnormalities, consisting of white matter T2 hyperintensities and cystic-appearing T1 hypointensities, were present in seven family members. The basal ganglia also showed cystic abnormalities. Neuropathologic examination in two cases revealed numerous lacunar infarctlike lesions, extensive demyelination, and widespread hyalinization of arteriolar walls with karyolysis and granular deposits within the media. These findings appear to constitute further evidence of a genetically determined arteriopathic leukoencephalopathy.

Binswanger encephalopathy is typically associated with hypertensive cerebrovascular disease; however, in recent years, largely due to advances in neuroimaging techniques, several families have been identified in whom an inherited vasculopathy was manifested primarily as subcortical dementia of the Binswanger type (1–7). Affected persons showed no evidence of systemic hypertension, cerebral amyloid angiopathy, or risk factors known to cause cerebrovascular disease. The condition is inherited as an autosomal dominant pattern and has been designated by the acronym CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) (8). Genetic linkage studies have shown evidence that the disease gene lies on the proximal short arm of chromosome 19 in a 2cM interval flanked by polymorphic markers D19S226 and D19S199 (9).

We describe a family of Central American ancestry in which some of its members are affected by a similar inherited form of Binswanger encephalopathy. Magnetic resonance (MR) imaging and neuropathologic examination of these family members documented marked leukoencephalopathy associated with distinct vascular changes.

Case Reports

Six family members in two generations were examined clinically and with MR imaging. MR imaging was performed in two others, adding a third generation, and, in one, a review of the medical records was done. Additional histories have been gathered from various other family members, so that, in all, the results span four generations (Fig 1). Two of the patients have died, the index case and his mother, and their brains were available for neuropathologic examination. [Authors' note: Subsequent to the acceptance of this article for publication, another family member (case 5) died, and his brain was also made available for complete neuropathologic examination. The gross and microscopic findings were essentially identical to those of the other two patients whose brains were examined.]

Case 1

Patient III-5, (the index patient), was the first family member studied. He was referred at the age of 52 years for evaluation of suspected multiple sclerosis. He had right-sided hemiparesis, left-central facial weakness, diffuse bradykinesia, retropulsion, truncal ataxia, and dementia. Reflexes were moderately hyperactive. The patient was disoriented to month, had decreased short-term memory, was unable to do serial 7's or 3's, and had marked spatial disorientation on drawing tests. A physical examination, including blood pressure and pulse, was otherwise normal.

CSF was clear, cell count was normal, protein was 40 mg/dL, and glucose was 74 mg/dL (serum, 110 mg/dL); it was negative for VDRL, myelin basic protein, immunoglobulins, and oligoclonal bands. A chemistry panel was normal, and vitamin deficiencies including B₁₂ and folic acid as a cause of leukoencephalopathy were eliminated. Hereditary leukodystrophies were ruled out with normal arylsulfatase, very long-chain fatty acids, anti-GM₁ ganglioside, β -galactosidase, and plasma urine amino acids. Thyroid studies, Lyme disease titer, and quantitative immunoelectrophoresis were all normal. HLA typing did not support demyelinating disease. Nerve conduction studies in the peroneal, posterior tibial, and sural nerves were unremarkable.

Computed tomography (CT) scans showed diffuse white matter disease and ischemic basal ganglia lesions. MR images, obtained 5 years apart, were markedly abnormal (Fig 2). The patient's neurologic condition deteriorated over 8 years, in a stepwise fashion, until his death from aspiration pneumonia. Autopsy was restricted to the brain only.

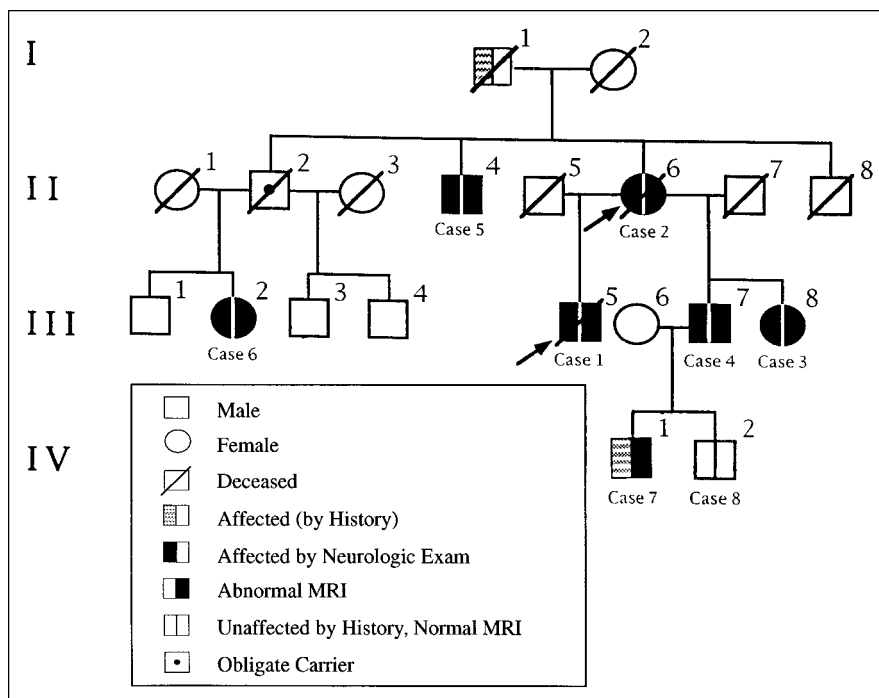
The right cerebral hemisphere was frozen and stored for molecular studies. The remaining tissue was fixed in neutral

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FIG 1. Pedigree of family with familial arteriopathic leukoencephalopathy. Arrows indicate the two members with neuropathology.



buffered 10% formalin, and sections were prepared for paraffin embedding. Sections were stained with hematoxylin-eosin and studied with the Gomori trichrome, elastic van Gieson, Loyez, Luxol fast blue-PAS, Congo red, and Holtzer methods. Immunostaining for actin and desmin was performed on selected sections. Some sections containing abnormal blood vessels were postfixed in 4% glutaraldehyde and processed for electron microscopy.

The whole brain weighed 1320 g. The vessels at the base, including the circle of Willis, were patent and free of atheroma. The ventricles were moderately dilated. The left centrum semiovale was attenuated and cavitated as a result of multiple cystic lesions, ranging from a few millimeters to 0.5 cm in diameter; many cysts were concentrated around blood vessels, and their confluence accounted for the collapse and shrinkage of major gyri, tracts, and corpus callosum. The arcuate fibers were relatively preserved. Multiple cystic spaces were also present in the basal ganglia, notably in the striatum.

Microscopically, the cystic lesions represented lacunae and infarcts of different chronological ages, generally remote. There was associated diffuse pallor of white matter due to severe loss of myelinated fibers with partial preservation of axons. Widespread changes in vessel walls were present: severe hyaline and hydropic degeneration of smooth muscle with nucleolysis; concentric sclerosis; Charcot-Bouchard microaneurysms; fibrinoid necrosis; and, rarely, elastosis with reduplication of elastic lamina, lipohyalinosis, and intimal fibrosis. These findings were most noticeable with the Gomori-trichrome stain, and involved both large (lateral lenticulostriate) and small intraparenchymal arteries. In most of these vessels, there was no trace of smooth muscle cells, and if present they were few and far between, enmeshed in collagenous tissue. A peculiar slate-gray substance often replaced the media (Fig 2). Immunohistochemical stains for specific muscle actin and desmin to confirm its derivation from smooth muscle were unsuccessful.

Electron microscopy disclosed electron-dense granular deposits throughout the media, corresponding to the slate-gray material noted with the trichrome stains. These deposits were extracellular, usually beneath the elastic lamina, and admixed with collagen (Fig 2).

Many of the small leptomeningeal arteries showed concentric sclerosis and stenosis, but the larger vessels were patent

and not as severely involved as comparably sized intraparenchymal arteries. In addition, loss of neurons, mainly in the zona compacta, and the frequent presence of Lewy bodies indicated concurrent idiopathic parkinsonism.

Case 2

Patient II-6, the mother of the index case, was referred at age 71 years. She was not hypertensive. She had mild bradykinesia and diffuse hyperreflexia in all four extremities, with flexor toe signs. She was mildly disoriented to date and place, unable to do serial 7's or 3's, and had severe spatial problems on drawing tests. Similar laboratory workup to case 1 was noncontributory. HLA genotyping, which included *A2,A24(9)*, *BW48,B44(12)*, *CW4*, and *DR4,DRW53,DQE3* with negative DNI, was nonrevealing. Spinal tap was traumatic, but a repeat was normal. A CT scan showed diffuse subcortical white matter disease and several basal ganglia lesions. An MR image was grossly abnormal (Fig 3). She gradually deteriorated and died 7 years later of aspiration pneumonia. Autopsy was restricted to the brain.

The brain weight was 960 g. As in case 1, there was minimal atherosclerosis with no significant luminal narrowing in the basal arteries and circle of Willis. Symmetric atrophy involved the frontal, parietal, and temporal lobes, in particular the paracentral regions. The centrum semiovale appeared semitranslucent, depressed, and softened, with focal areas of marked cystic degeneration, especially involving the right parietal region. The basal ganglia had a spongy appearance and contained several small lacunae. Wedge-shaped old infarcts were present in the right parietal and frontal cortices (Fig 3).

Histologically, the findings were quite similar to those seen in the index case, including the smooth muscle changes and the amorphous/granular material replacing the media of the intraparenchymal arteries. Ultrastructurally, the abnormal material in the vessels was also identical to that of the index patient.

Case 3

Patient III-8 was first examined at age 49 years; she had a history of migraine with visual auras since her teens. She experienced transient sensory symptoms in the right upper extremity, dysarthria, and imbalance unrelated to the migraine headaches. Blood pressure was 160/95. A neurologic examina-

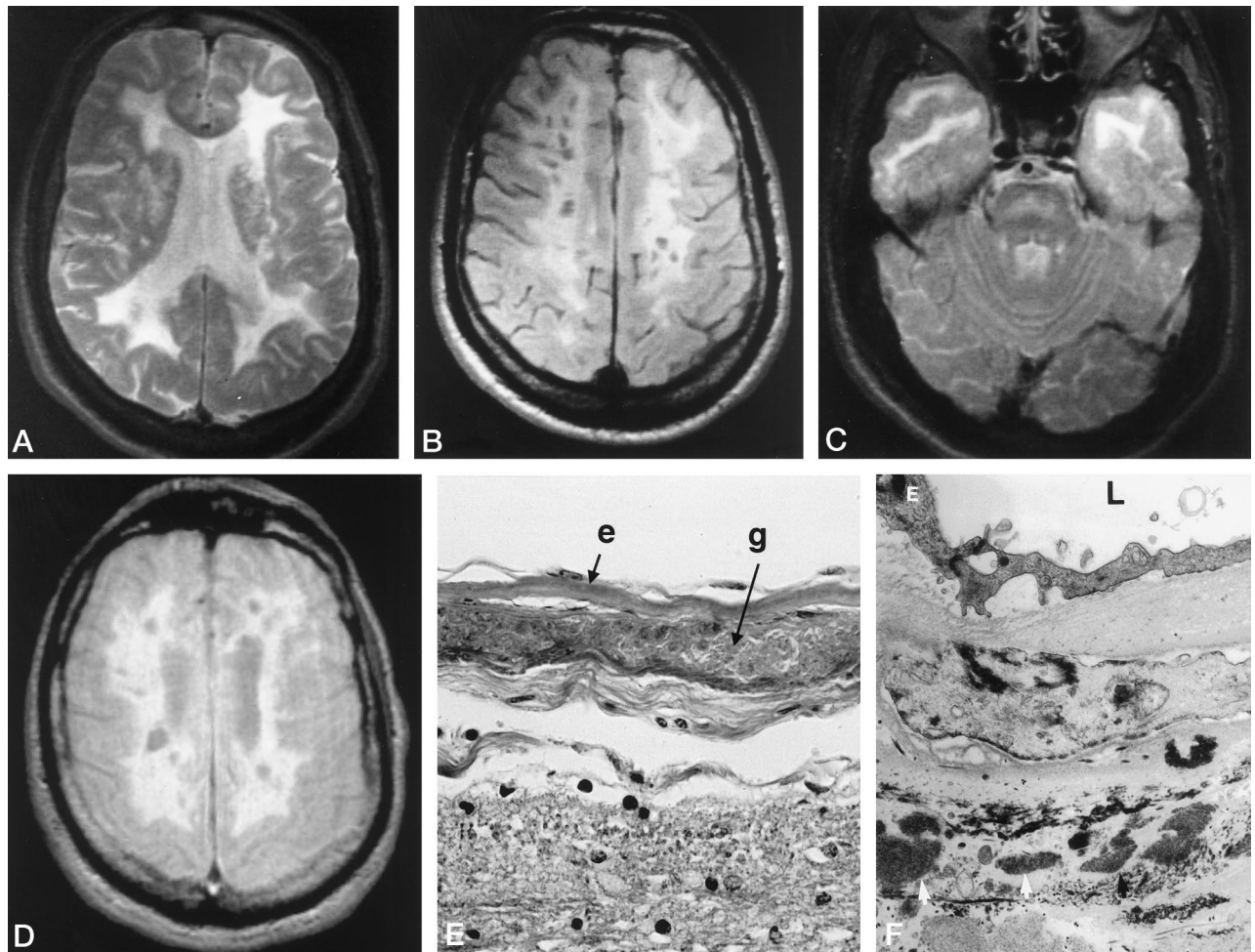


FIG 2. Case 1 (index patient): MR and pathologic findings.

A, Axial T2-weighted (2000/80/2) image at the level of the lateral ventricles shows extensive hyperintense white matter abnormalities extending from the ventricular surface to the cortical boundary.

B, Axial proton density-weighted (2000/40/2) image shows multiple fluid-filled cysts within the demyelinated white matter. These cysts were also visible on T1-weighted images.

C, Axial T2-weighted (2000/80/2) image at the level of the pons shows extensive pontine and anterior temporal lobe involvement. No cerebellar involvement was noted.

D, Axial proton density-weighted (2000/30/1) image 5 years later, and 3 years prior to death, is somewhat degraded by tremor but shows confluent demyelination of the deep and subcortical white matter with multiple fluid-filled cysts. Allowing for positional differences, the findings are similar to the initial study.

E, Microscopic pathologic section of intraparenchymal medium-sized artery shows granular degeneration of its media (g); e indicates thickened elastica (Gomori trichrome, original magnification $\times 40$).

F, Electron micrograph shows focal granular osmiophilic deposits (arrows) in the wall of an intraparenchymal vessel. E indicates endothelial cell; L, vascular lumen (original magnification $\times 7000$).

tion was normal except for anisocoria. Subsequent examination 1 year later disclosed disorientation to date and an inability to do serial 7's or 3's or to copy a cube. Diffuse but asymmetric hyperreflexia developed, with equivocal extensor toe responses. Blood pressure was 150/88. Previous routine laboratory studies were unremarkable. No additional tests were done except for two MR studies of the brain, 5 years apart, which were markedly abnormal (Fig 4).

Case 4

Patient III-7 was examined at age 47 years. He reported memory problems and marked emotional lability. His history was significant for an illness at age 21 that was accompanied by paralysis of the right side of his face and the right arm, lasting about 6 months, and memory impairment, purportedly due to measles encephalitis. There was no history of migraine or

hypertension. Neurologic examination revealed minimal abnormal attention span and marked symmetric hyperreflexia but no Babinski responses. No tests were done except for a brain MR examination, which was markedly abnormal (Fig 5). He has experienced slowly progressive worsening of his neurologic problems.

Case 5

Patient II-4, age 76, initially examined in 1992, had a long history of neuropsychiatric disease, variously labeled as schizophrenia, manic-depression, organic brain syndrome, and olivopontocerebellar degeneration. He has been severely disabled for the past 15 years, requiring institutional care. His condition, which has remained relatively stable for the past 4 years, includes sensorineural hearing impairment, moderate dementia with bradyphrenia, bradykinesia, rigidity and spasticity with diffuse hyperreflexia, and bilateral Babinski responses.

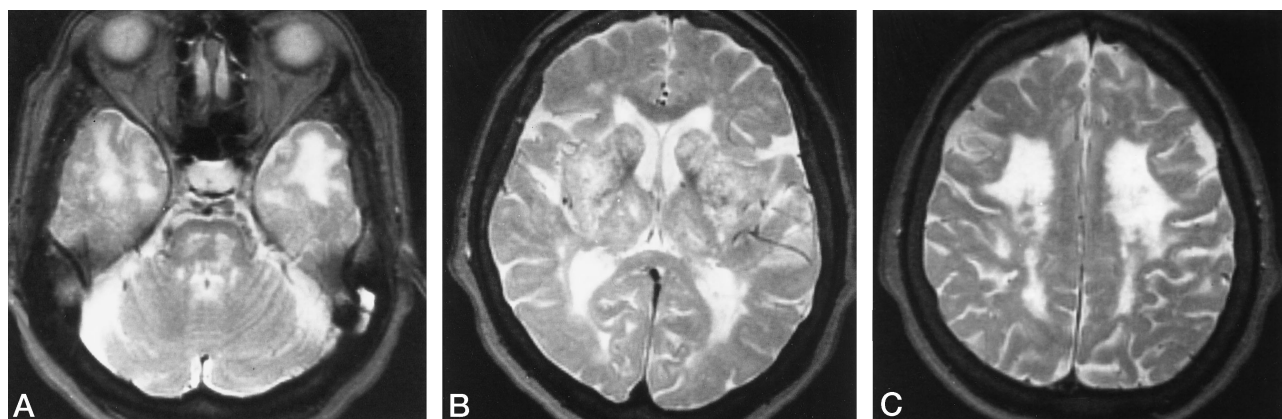
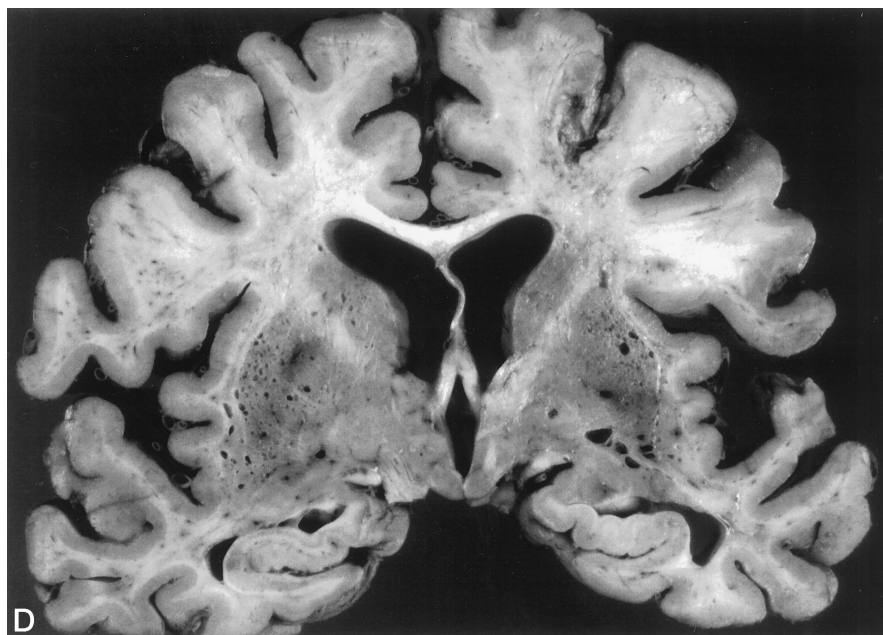


FIG 3. Case 2.

T2-weighted (2000/80/2) images show extensive hyperintense abnormalities in pons, temporal lobes, and basal ganglia (A and B), with confluent bilateral white matter hyperintensities present in the centrum semiovale (C).

D, At gross pathology, coronal section of brain shows bilateral atrophy and grayish discoloration of the centrum semiovale and internal capsule. Note sievelike appearance and état lacunaire of both basal ganglia.



He has been ambulating with the assistance of two people. Laboratory studies, including serum lactate level, were unremarkable. A brain MR examination was abnormal (Fig 6).

Case 6

Patient III-2 was initially examined at age 53 years. There is some question as to whether her diagnosis is consistent with that of the rest of the family. The current diagnosis, based on the findings of several biopsies of active skin lesions, is vasculitis caused by lupus/Sjögren syndrome. A neurologic examination revealed decreased sensation to pin and light touch diffusely in the right lower extremity, but normal strength and reflexes. Brain MR findings were minimally abnormal, with a single subcortical white matter lesion in the right hemisphere. Her father, an obligate carrier, had angina and died at age 57, but had no known history of dementia or neurologic abnormalities.

Cases 7 and 8

Two other, much younger, family members have not been examined clinically but have been studied by MR imaging. One (case 7, IV-1) had abnormal findings (Fig 7) 1 year after a normal baseline study. The other (case 8, IV-2) had a normal MR examination at age 21 years.

The Table summarizes the MR features in all eight cases.

The paternal progenitor of all these patients, I-1, was a highly respected professional who died in his mid-40s in San Salvador with progressive dementia and a gait disorder. No autopsy was done, and medical records and information about his forebears are not available. His wife was not known to have neurologic problems.

Discussion

The clinical, neuroradiologic, and neuropathologic findings in the index patient and his mother are similar to those found in Binswanger encephalopathy, with important exceptions. The condition was familial; involved no concurrent history of risk factors, including hypertension; manifested exceptional MR imaging features; and exhibited distinct vascular pathologic findings. In recent years, largely due to advances in neuroimaging techniques, notably MR imaging, several families with a similar disorder have been identified. Most of these reports originated from Europe, under different titles: CADASIL (7, 8, 10–12), familial leukoencephalopathy with subcortical ischemic strokes (6), hereditary multiinfarct dementia

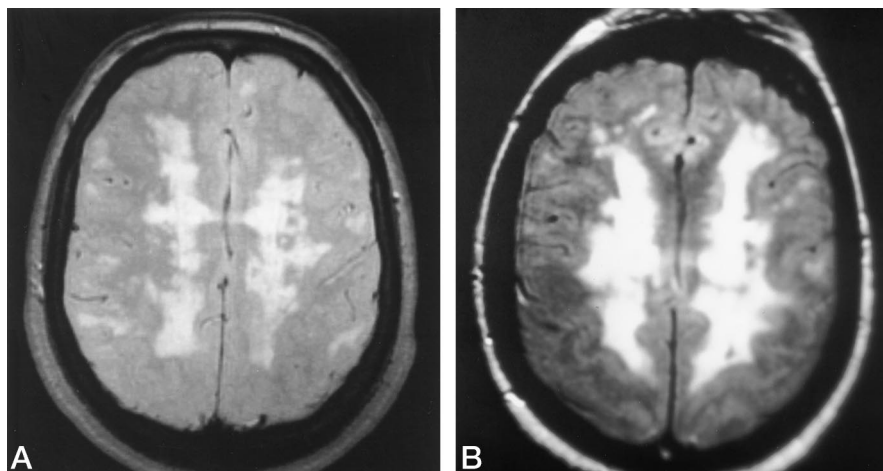


FIG 4. Case 3.

A, Axial proton density-weighted (2000/40/2) image at the level of the centrum semiovale shows confluent white matter and corpus callosum lesions.

B, Axial proton density-weighted (2500/30/1) image 5 years later shows progression in size and extent of lesions, paralleling the patient's clinical deterioration.

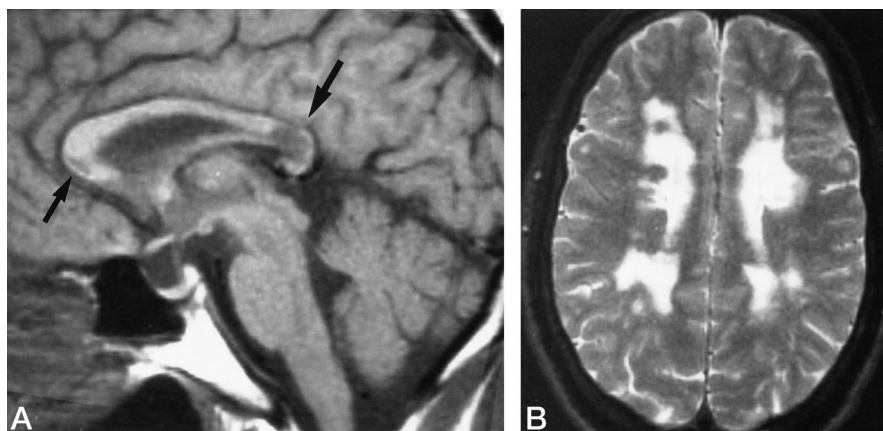


FIG 5. Case 4.

A, Sagittal T1-weighted (400/20/2) image shows a large destructive lesion in the splenium of the corpus callosum (large arrow) and a smaller one in the genu (small arrow).

B, Axial T2-weighted (2500/80/1) section through centrum semiovale shows characteristic confluent white matter hyperintensities, which were out of proportion to the patient's moderate neurologic deficits.

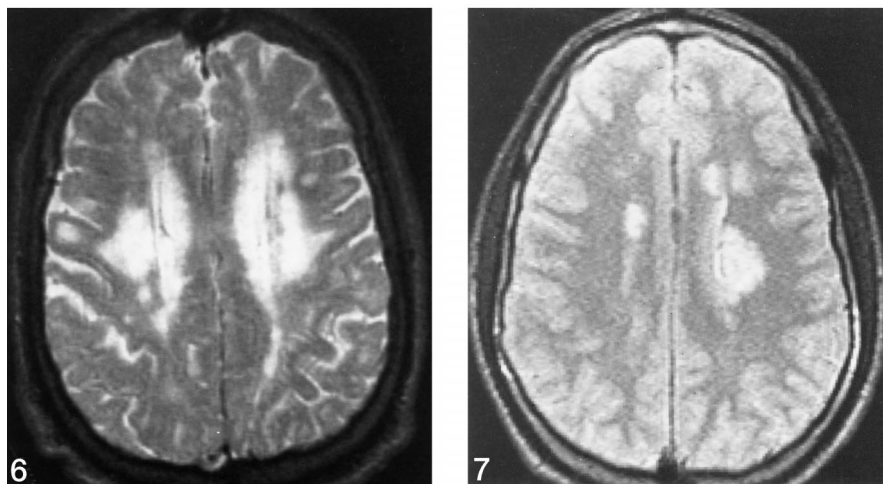


FIG 6. Case 5: Axial T2-weighted (2000/80/1) image shows confluent periventricular and corona radiata hyperintensities. Early subcortical white matter involvement is also noted.

FIG 7. Case 7: T2-weighted (3000/64/2) image at the level of the centrum semiovale in this symptomatic patient shows multiple periventricular hyperintense lesions, left greater than right. One year earlier, the MR image had been normal.

(13, 14), familial encephalopathy of Binswanger type without hypertension (3–5), autosomal dominant arteriopathic leukoencephalopathy (15, 16), and small arterial granular degeneration in familial Binswanger syndrome (17). Additionally, there are sporadic cases with a similar constellation of findings, including the peculiar vascular changes that characterize this condition, called sclerosing vasculopathy of the central nervous system (2) and agnogenic medial arteriopathy (18).

In our series, as in previous reports, the disease

spans a wide range of ages. However, there was a tendency for the patients to be younger than those with Binswanger encephalopathy. The clinical manifestations also varied, but they often followed a progressively downward neurologic decline, usually beginning as subcortical dementia that subsequently was aggravated by episodes of acute or subacute stroke-like attacks. Our index case also had idiopathic parkinsonism, which explains some of the extrapyramidal manifestations that arose during the course of his illness.

Sites of involvement of familial arteriopathic leukoencephalopathy on MR images

Case	Age/Sex	Generation	Centrum Semiovale White Matter	Temporal Lobe White Matter	Pons	Corpus Callosum	Caudate	Thalamus	Lenticular Nucleus	External Capsule	Macrocyts
1*	52/M	III-5	+++	+++	++	—	+++	+	+++	+	+++
2	71/F	II-6	+++	+++	++	—	+++	++	+++	++	++
3†	49/F	III-8	+++	+++	+++	+	—	—	+	++	+
4	47/M	III-7	++	+	+	+	—	—	+	—	—
5	67/M	II-4	+++	++	++	—	+	++	++	++	++
6	53/F	III-2	+	—	+	—	—	—	—	—	—
7‡	19/M	IV-1	++	—	—	—	—	—	—	—	—
8	21/M	IV-2	—	—	—	—	—	—	—	—	—

* Two MR studies 5 years apart had identical findings.

† Two MR studies 5 years apart showed interval progression.

‡ Two MR studies 1 year apart showed marked progression.

Note.—+++ indicates severe involvement; ++, moderate involvement; +, mild or few lesions; —, no involvement.

While the MR features in these family members resembled those described in severe leukoencephalopathy of the Binswanger type, there were differentiating features that may prove to be of diagnostic and prognostic value. Several members of this family had very severe MR changes at a relatively young age. Also, the involvement of the white matter of the anterior temporal lobes was unlike the typical Binswanger leukoencephalopathy or that described in cerebral amyloid angiopathy (19–24). Basal ganglia involvement in our cases was even more severe than the usual MR appearance in Binswanger encephalopathy. The macrocystic infarcts were unusual and distinctly different from the usual lacunar disease seen in the basal ganglia of chronically hypertensive patients. Involvement of the corpus callosum, as in two of our patients, is unusual for hypertensive vascular disease. In combination, these MR features help to distinguish this entity from other demyelinating and ischemic diseases, especially if found in a patient without hypertension or cardiovascular risk factors.

Pathologically, as in typical hypertensive Binswanger encephalopathy, the white matter was most severely affected and contained multiple lacunae; however, small and large cortical infarcts were not as common as seen in hypertensive Binswanger encephalopathy. The vascular changes exhibited one feature not found in brains of hypertensive patients with Binswanger encephalopathy; namely, the granular/amorphous deposits in the media (18, 25, 26). Although marked loss of smooth muscles in small cerebral arteries occurs in patients with long-standing hypertension, the medial granular material found in our cases and previously documented by others was quite distinct. This material appeared ultrastructurally as a finely granular or amorphous electron-dense substance bearing no resemblance to elastin, fibrin, amyloid, or lipid. Its source and nature remain enigmatic, but most likely it represents degradation products of degenerated smooth muscles.

As in other reported cases of familial nonhypertensive Binswanger encephalopathy, the pattern of inheritance in this family is consistent with autosomal

dominant transmission. Tournier-Lasserre et al (8) reported a strikingly similar disorder, which they referred to by the acronym CADASIL. They initially demonstrated linkage of the CADASIL locus to a 14cM interval on the short arm of chromosome 19, and subsequently refined the critical region to the 2cM interval between polymorphic markers D19S226 and D19S199 (9). More recently, the same investigators have identified mutations of notch 3 mapped to the CADASIL-critical region on chromosome 19 (27). We are currently actively studying the genetic linkage of this family to determine whether it is similar to that described by Tournier-Lasserre and her group.

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