Idiopathic progressive hyalinizing and calcifying CNS vasculopathy

Article abstract—We present a female adolescent with intermittently progressive neurologic deficits over a period of 7 years. Serial imaging studies showed a calcifying lesion with increasing enhancement, signal abnormalities from the subcortex to the medulla, and hemispheric volume loss. Stereotactic biopsies disclosed a hyalinizing and calcifying vasculopathy involving the penetrating vessels. The vasculopathy may result in ischemic lesions responsible for the severe deficits.

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Cerebral vascular hyalinization and parenchymal calcification may occur in various systemic and neurologic diseases, and with several idiopathic cerebral vasculopathies. We discuss the case of a unique intermittently progressive hyalinizing and calcifying CNS vasculopathy of uncertain etiology.

Case report. The patient is a young woman without prior medical history or family history of neurologic or systemic diseases. Her parents are Puerto Rican, unrelated, and both living. The only sibling, a 28-year-old man, has no medical problems. There were no difficulties during the pregnancy, delivery, or early development of the patient.

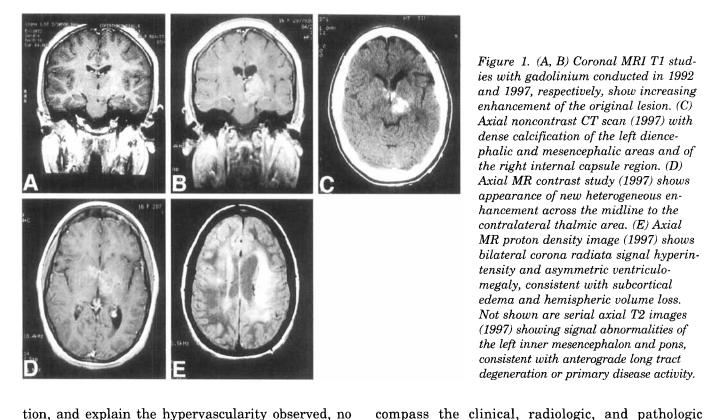
The patient originally presented at age 11 with difficulty ambulating and right leg paresis. MRI revealed enhancement of the left thalamic area and mild mass effect on the third ventricle. Stereotactic biopsy was complicated by hemorrhage, causing hemiparesis, and histologic evaluation demonstrated numerous small-caliber, thick-walled, hyalinized vessels with scattered parenchymal mineralizations. The vessels had an abnormal density suggestive of a malformative process but did not display features typical of capillary, venous, cavernous, or arteriovenous malformations. Over the next 2 years, hyperemotionality and dysarthria developed.

Five years later the patient complained of gait unsteadiness. Examination showed emotional lability, pseudobulbar dysarthria, upbeat nystagmus, right arm hypesthesia, right spastic hemiparesis, and left dysmetria and dystaxia. A transient left internuclear ophthalmoplegia was observed. Imaging studies showed dense calcification in the area of the original lesion, extension of enhancement, and diffuse signal abnormalities from the centrum semiovale to the pons (figure 1, A through E). Serum chemistry, hematology, erythrocyte sedimentation rate, antinuclear antibody, antineutrophil cytoplasmic antibody, pituitary and parathyroid hormone levels, angiotensin converting enzyme, serum protein electrophoresis/immunoglobulin protein electrophoresis, and lactate were normal. CSF chemistry, cell counts, Venereal Disease Research Laboratory, Lyme titers, immunoglobulin G synthetic rate, and oligoclonal bands were also normal, whereas cytology noted few normal and reactive lymphocytes. EEG showed general disorganization with left delta and right theta frequencies. Thoracoabdominopelvic contrast CT, total body gallium scan, hepatic sonogram, naso-oropharyngoscopy, and fecal guaiacs were negative. Ophthalmologic consult was noncontributory. Muscle, dermal, and nerve biopsies were normal, and electron microscopic examination of the muscle and its mitochondria yielded no abnormalities. Muscle mitochondrial enzyme analysis was normal. No HIV or other viral testing was performed.

At age 17 the patient developed lethargy, bowel and bladder incontinence, dysphagia, and progressive imbalance. Apathy, decreased memory and intellect, poor palate elevation with absent pharyngeal reflex, palatal tremor, and increased ataxia were noted on examination. MRI showed extension of abnormal signal to the central pons and medulla bilaterally and new signal changes in the cerebellar peduncles. Diffusion study conducted several days later was normal, and cerebral angiogram was negative. Endocrine, metabolic, and genetics consults were unrevealing. Repeat biopsy (figure 2) of the left diencephalic region showed vascular changes similar to, but more pronounced than, the previous biopsy. Hyalinization obliterated normal vascular structure such that elastica could not be visualized. Rosenthal fibers and mineralization were prominent. There was no evidence of inflammation, plasma or erythrocyte extravasation, or spheroids. Changes typical of cerebral autosomal dominant arteriopathy (CADASIL) were absent. Hyalinized vascular regions did not react with PAS, Thioflavin S, and Congo Red stains. Perl's stain revealed focal iron deposition in mineralized regions. Material was insufficient for examination by electron microscopy. Decadron (Merck & Co., West Point, PA), 4 mg every 6 hours for 9 days, tapered off over 7 days, had no beneficial effect.

A year later the patient developed seizures and temporarily lapsed into a comatose state. Severe permanent deficits in mentation persist.

Discussion. CNS microvascular hyalinization typically occurs in hypertension, diabetes, and as an age related change¹ and is often present in cases of lupus vasculopathy, amyloid angiopathy, CADASIL, and vascular malformations.² Diencephalic calcification may occur in many disease states, including parathyroid disorders, idiopathic familial cerebral calcification (IFCC), mitochondrial diseases, and cerebral lupus.² However, in this patient, endocrinologic and metabolic evaluations excluded a disorder of calcium metabolism, and there was no family history of IFCC. Muscle biopsy and mitochondrial analyses provided no evidence for a mitochondrial disease, and the absence of systemic manifestations, and consistently negative serologic tests, excluded the possibility of systemic lupus erythematosis. Although a vascular malformation may calcify, cause hyaliniza-



tion, and explain the hypervascularity observed, no malformation was identified on biopsy, and any neovascularization present may be caused by chronic local ischemia from any cause.³ Diagnostic consideration was especially given to angiopathic processes such as amyloidosis and sporadic nonfamilial CADA-SIL, but histologic specimens failed to stain for amyloid and did not reveal changes classically present in CADASIL.

Literature review demonstrates several idiopathic, hereditary and nonhereditary, cerebral vasculopathies that may be considered in the differential diagnosis, but none of which adequately en-

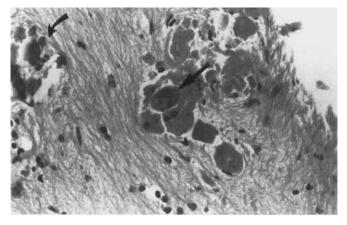


Figure 2. High-power photomicrograph shows small to moderate caliber vessels with remarkably thickened, hyalinized walls and severe luminal narrowing with occlusion. Focal vascular mineralization (straight arrow) and parenchymal mineralization (curved arrow) is also seen in the surrounding gliotic neural parenchyma. (H-E stain, magnification $\times 100$ before 38.4% reduction).

broretinal vasculopathy (HCRV),4 hereditary endotheliopathy with retinopathy nephropathy and stroke (HERNS),⁵ and retinocochleocerebral vasculopathy $(RCCV)^6$ may resemble this case radiologically via diffuse signal abnormalities and foci of enhancement on MRI. RCCV, although pathologically heterogeneous, may partially resemble this case histologically-arteriolar thickening and hyalinosis. HCRV and HERNS differ from the current case by autosomal dominant inheritance and by the characteristic presence of vascular fibrinoid necrosis in the former and multilamelated vessel basement membrane in the latter. All three differ from this case in that retinal or systemic (renal in HCRV and

possible myopathy in RCCV) symptoms are cardinal features, and that cerebral mineralization is absent. A peculiar, fatal, autosomal recessive vasculopathy associated with alopecia, lumbago, spondylosis deformans, dementia, pyramidal and extrapyramidal motor symptoms, and accelerated systemic and cerebral arteriosclerosis clearly differs from this one.⁷ A novel microangiopathy characterized by angiomatous vessels and diffuse cerebral calcification and cyst formation is also readily distinguished.⁸ Nonchromosome 19 CADASIL variants and other hereditary leukoencephalopathies fail to exhibit the important features of the current case.^{9,10}

aspects of this particular patient. Hereditary cere-

Figure 1. (A, B) Coronal MRI T1 studies with gadolinium conducted in 1992 and 1997, respectively, show increasing enhancement of the original lesion. (C) Axial noncontrast CT scan (1997) with dense calcification of the left diencephalic and mesencephalic areas and of the right internal capsule region. (D) Axial MR contrast study (1997) shows appearance of new heterogeneous enhancement across the midline to the contralateral thalmic area. (E) Axial MR proton density image (1997) shows bilateral corona radiata signal hyperintensity and asymmetric ventriculomegaly, consistent with subcortical edema and hemispheric volume loss. Not shown are serial axial T2 images (1997) showing signal abnormalities of the left inner mesencephalon and pons, consistent with anterograde long tract degeneration or primary disease activity.

The absence of any obvious etiology to explain the development of the vascular hyalinization and parenchymal calcification, and the inability to classify the disease process among previously described vasculopathies, raises the possibility that this case may represent a CNS vasculopathy not yet described in the neuropathologic literature.

Several aspects of this case assist in characterization of the vasculopathy. Radiologically, the increasing enhancement and edema evident on imaging studies suggests ongoing compromise of the CNSvascular barrier and a progressive defect at the level of the microvasculature. The fact that the enhancement and signal abnormalities are limited to the deep subcortical and inner brainstem regions suggests that disease activity is restricted to the terminal arterioles and venules, sparing the larger vessels. The negative angiogram attests to the normality of the macrovasculature, yet allows for the possibility of a vascular abnormality affecting the penetrating vessels whose caliber is below angiogram resolution capabilities. Histology confirms involvement of the deep penetrating vessels but is unable to determine whether the hyaline and calcium changes are part of the primary disease process or a secondary manifestation. Given that the patient's deficits are for the most part intermittent and acute in onset, it is probable that the clinically evident neurologic deterioration is at least partially caused by periodic repeated ischemic events, possibly superimposed on chronically ischemic tissue. The volume loss seen on imaging studies supports an ischemic process, and the vascular hyalinization with luminal compromise provides a basis for this premise. Diffusion MRI may have been performed too late to detect the infarcted tissue. Parenchymal mineralization may also have a role in the observed neurologic deficits by direct deposition and local tissue destruction.

We hypothesize that the pathologic process creates profound hyalinosis and structural alterations of penetrating vessels in subcortical and brainstem areas, causes marked parenchymal mineralization, and has an ischemic basis for the observed clinical deficits.

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