

Cavernous Hemangioma of the Retina

A Four-Generation Pedigree With Neurocutaneous Manifestations and an Example of Bilateral Retinal Involvement

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● **Cavernous hemangioma of the retina is an unusual vascular hamartoma whose coexistence with vascular anomalies of the skin and central nervous system has been recognized recently. A 39-year-old woman, who had an acute palsy of the right third cranial nerve, had a history of seizures, cutaneous vascular anomalies, and a cavernous hemangioma of the retina of the right eye. One of her daughters demonstrated bilateral retinal cavernous hemangiomas, and another daughter, who developed seizures when febrile, displayed cutaneous vascular anomalies. A four-generation pedigree showed a number of cutaneous vascular anomalies, seizures, and stroke-related deaths. The pedigree suggests further support for considering this disorder an authentic oculoneurocutaneous triad.**

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Cavernous hemangioma of the retina is a rather rare lesion that has been associated recently with vascular anomalies in the skin and central nervous system.¹⁻⁴ This retinal hamartoma may vary in appearance from a rather uncomplicated collection of aneurysms to an elaborate, sessile, grape-like, thin-walled, often clustered complex of red globules, at times projecting into the vitreous cavity with a three-dimensional quality. Gray-white material, the exact nature of which remains ill-defined, may

participate in the structure of this lesion. Smaller aneurysms may be grouped near the major malformation, and both the course and caliber of the afferent and efferent vessels appear unaltered.

In contrast to retinal capillary hemangiomas and retinal telangiectasias, this lesion is not associated with appreciable exudation, and marked leakage of fluorescein is not considered to be a characteristic angiographic property. Spontaneous hemorrhage can occur, particularly from the larger lesions.

These hamartomas are frequently multiple and capable of simultaneous involvement of multiple organ systems. This article describes a four-generation pedigree in which the multisystem nature of cavernous hemangioma is implied, and an unusual occurrence of bilateral retinal lesions is demonstrated. To the best of our knowledge, this is only the fourth bilateral case reported in the ophthalmic literature.

REPORT OF CASES

The proband was a 39-year-old woman with a lifelong history of seizures (currently controlled by phenytoin and phenobarbital), who, in July 1976, fell and struck her head with no concomitant loss of consciousness. One month later she awoke with diplopia and came to us with a total right third nerve paralysis. There was also a questionable paresis of the right fourth nerve. She reported no history of intracranial noises, the conjunctival vessels were not engorged, no bruit was detected over the right orbit, and the corneal sensitivity in the right eye was considered within normal limits. The visual acuity was 20/20 + 2 in the right eye and 20/15 in the left eye.

The contributory fundus findings were limited to the superonasal quadrant of the right eye, where a linear, radially oriented formation of rather fine saccular alterations in the retinal angioarchitecture was noted (Fig 1). A representative selection from the angiographic sequence (Fig 2)

demonstrated fluorescein-plasma/erythrocyte layering within these aneurysms, reflecting the stagnant blood flow.

Physical examination revealed cutaneous vascular anomalies of the capillary variety at the midline in the lumbar region that, by history, were unchanged since birth (Fig 3).

Appropriate neurosurgical consultation, as well as skull x-ray films, a brain scan, and computerized axial tomography (CT scan) were obtained. The CT scan showed a small, deep-seated left posterior temporal lobe calcification with no signs of a mass lesion around it. The EEG showed a possible left frontal focus of seizure activity. Arteriograms disclosed a slight straightening and elevation of the left posterior cerebral artery, but even with bone-subtraction studies, a vascular tumor could not be detected. A pneumoencephalogram was normal. Ultrasonography of both globes and orbits was normal.

There was a familial history of diabetes (proband's father) and a five-hour glucose tolerance test was obtained. Results at fasting were 88 mg/dL; 115 mg/dL at 30 minutes; 120 mg/dL at one hour; 89 mg/dL at two hours; 61 mg/dL at three hours; 70 mg/dL at four hours and at five hours; urine results, negative at fasting, 30 minutes, and five hours; +4 at one and two hours; +2 at three hours; and "trace" at four hours.

Visual fields (tangent screen) in November 1976 were normal, and by December the diplopia had cleared.

In September 1977, this patient had a migraine headache, and she was examined by her neurosurgeon for frequent headaches and transient episodes of diplopia. In November 1977, the patient experienced another episode of ptosis (right eye) and diplopia, but she was unavailable for our subsequent examination.

In March 1978, the neurosurgeon recorded that the proband's right pupil was dilated and fixed, but that the diplopia had responded to methylprednisolone (Medrol), 4 mg four times a day.

This patient's 10-year-old daughter had a visual acuity of 20/20— bilaterally. Ophthalmoscopy showed a cavernous hemangioma of the retina involving the inferonasal quadrant of the right eye (Fig 4, top) and a somewhat smaller lesion in the su-

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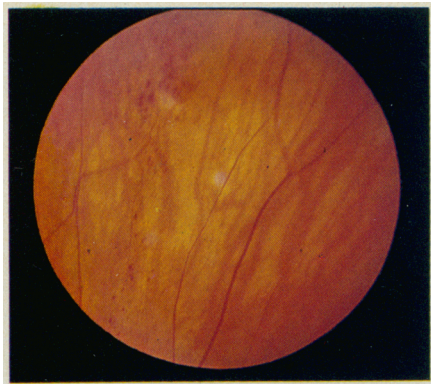


Fig 1.—Cavernous hemangioma of retina in right eye of proband. Note radially oriented configuration of aneurysms in superior nasal quadrant.

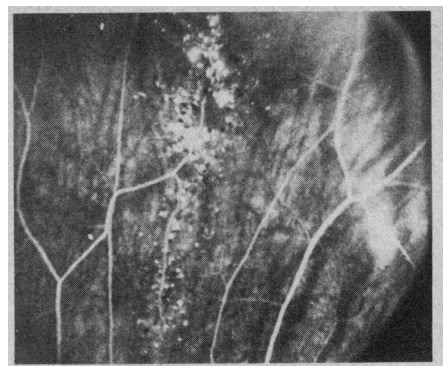


Fig 2.—Representative selection from angiographic sequence of hamartoma in proband's right eye demonstrates fluorescein-plasma/erythrocyte layering within saccules.

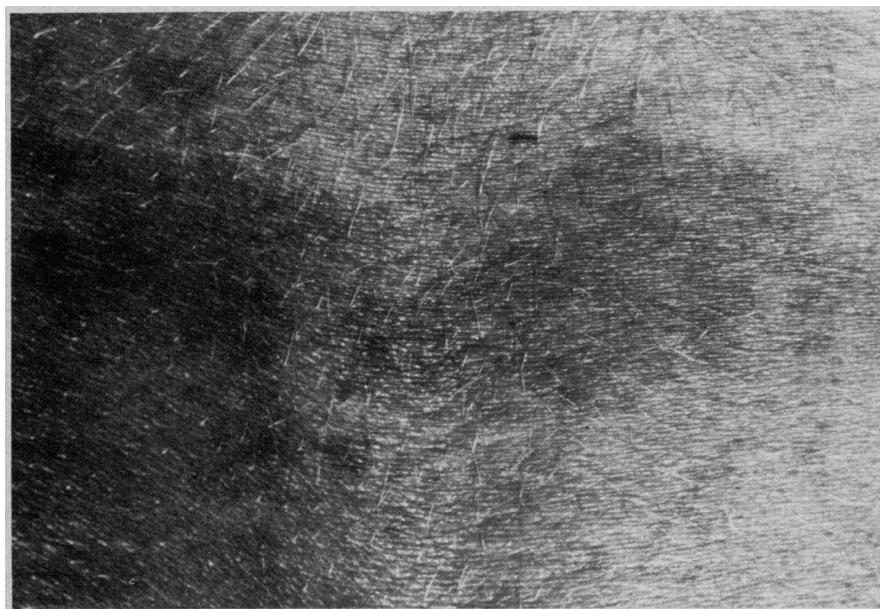


Fig 3.—Cutaneous vascular anomaly of capillary variety in midline of lumbar region of proband.

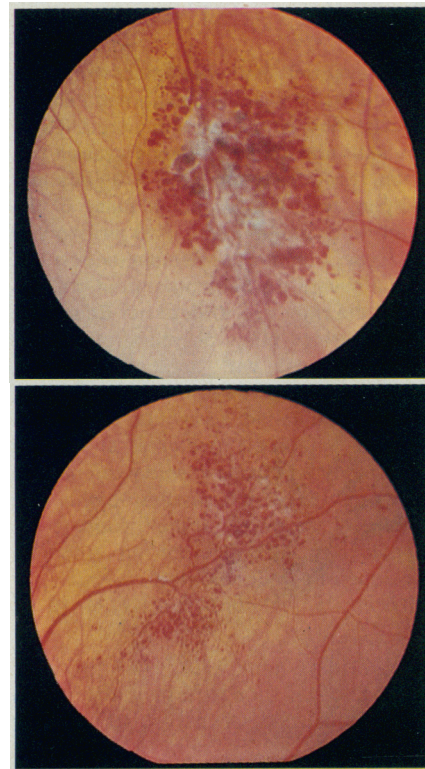


Fig 4.—Top, Ten-year-old girl with sessile cavernous hemangioma of retina in inferior nasal quadrant of right eye. Bottom, Left eye of same child demonstrates cavernous hemangioma of retina in superior temporal quadrant.

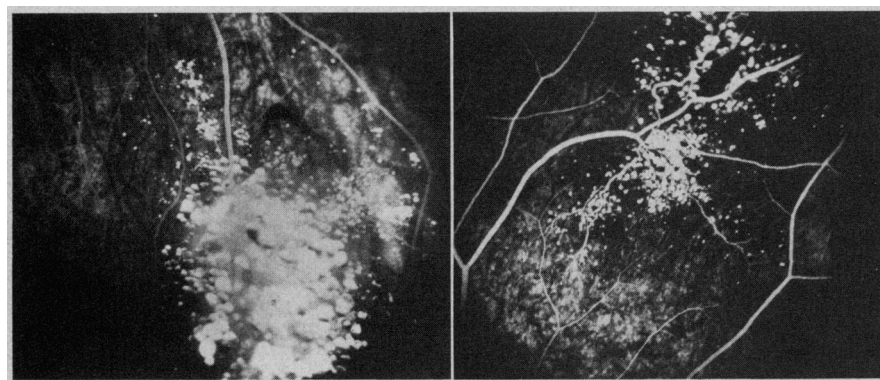


Fig 5.—Left, Angiographic field in 10-year-old child's right eye demonstrates plasma-erythrocyte layering within aneurysms and some diffusion of dye into overlying vitreous. Right, Fluorescein sequence of left eye demonstrates plasma-erythrocyte separation.

perotemporal quadrant of the left eye (Fig 4, bottom).

Fluoroangiography of the right eye revealed plasma-erythrocytic layering within the ovoid aneurysms and, late in the sequence, some diffusion of dye into the overlying vitreous (Fig 5, left). Perfusion of the hamartoma was incomplete. In the

left eye the angiogram also demonstrated plasma-erythrocyte separation within the vascular lesion (Fig 5, right).

The proband had another daughter who underwent a neurologic evaluation when she was 3 years of age. At that time she displayed multiple congenital abnormalities, including poor configuration of the

hands, defective gross motor coordination, impaired speech, and, by history, febrile grand mal seizures. Findings on her karyotype and amino acid studies were within normal limits. Skull x-ray films were normal, with the exception of possible hypertelorism. Roentgenograms of the hands revealed mild incurvation of the little fingers. The distal phalanges of both fingers and thumbs were hypoplastic with multiple ossification centers that caused several of them to be somewhat elongated. The EEG was reported as normal. When seen at age 7 years, this daughter's visual acuity was 20/20 in both eyes. The fundi were normal, but she demonstrated cutaneous hemangiomas of the lower part of the back similar to those of her mother.

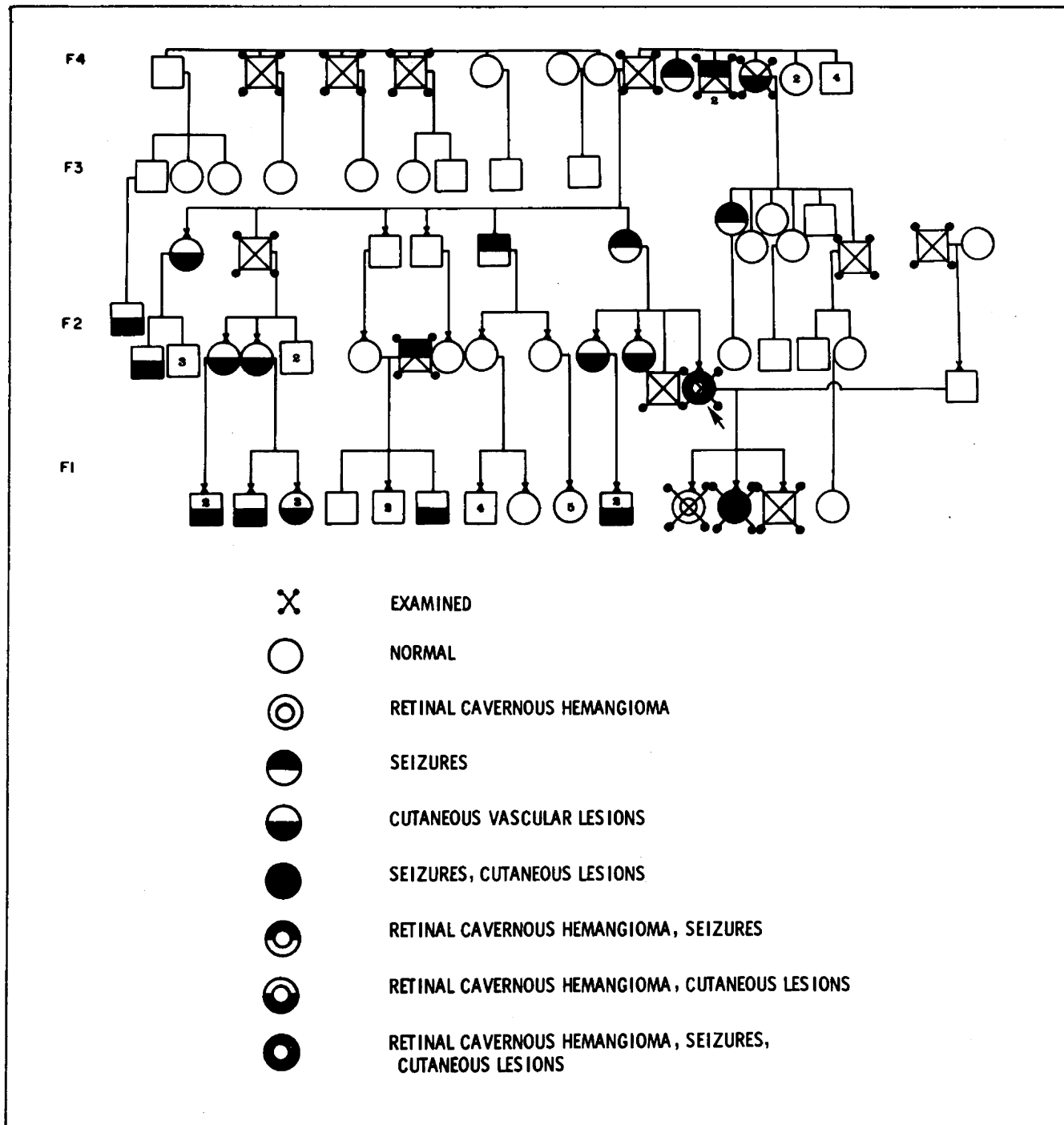


Fig 6.—Pedigree spanning four generations and consisting of 90 persons. Arrow indicates proband. Numbers indicate number of persons a given symbol represents. Circles are females, and squares are males.

A pedigree spanning four generations was constructed, and this consisted of 90 persons. We examined the proband, her three children, and 11 other persons listed in the pedigree. They received ocular examinations as well as examination for cutaneous vascular lesions. They were also questioned for a history of either grand mal or petit mal seizures (Fig 6). We did not examine and question the remaining persons in this pedigree, but, where possible, informal information was gained from other family members.

COMMENT

The multisystem expression of this disorder has been difficult to evaluate. Cutaneous vascular hamartomas occur commonly in the normal population, and their presence in patients with cavernous hemangioma of the retina may prove to be a chance occurrence.³ Nevertheless, the patient described here and the associated pedigree suggest inclusion of the syndrome of

cavernous hemangioma of the retina (and/or optic nerve), cutaneous angio-
ma, and cavernoma of the cerebrum
and brainstem in the category of pha-
komatoses.

In 1971, Gass presented evidence that cavernous hemangioma of the retina and optic nerve head is a specific vascular hamartoma to be differentiated from other vascular malformations including retinal telangiectasis, angiomatosis retinae, and racemose

angioma.^{2,3} He reviewed three cases and referred to reports of nine additional patients with ophthalmoscopic lesions suggestive of a similar disorder. Two additional cases are cited in his addendum.²

In their review of this subject, Lewis et al related the details of three cases of cavernous hemangioma of the retina and noted the presence of 34 previously reported cases of this rare malformation. They also mentioned an additional case in their addendum.¹

The proband's retinal vascular malformation consisted of a linear collection of aneurysms. Her daughter's retinal hamartomas consisted of rather localized, sessile retinal vascular malformations composed of clusters of saccular aneurysms filled with blood of variable color. In this child, the thin-walled globules appeared to arise from a retinal vein, and isolated clumps of aneurysms surrounded the body of the lesion. The course and diameter of the afferent and efferent retinal vessels were generally unaffected. Although most cavernous hemangiomas of the retina show no appreciable leakage of fluorescein, one of our patients showed some late diffusion of dye into the overlying vitreous. Fluorescein-plasma/erythrocyte layering within the saccular aneurysms suggested delayed perfusion (Fig 2). A gray-white substance suggesting fibrous tissue and partially obscuring the underlying angioarchitecture was evident in one malformation (Fig 4, left).

The above description of our patients concurs with the accounts of Gass and Lewis et al, who reviewed the history, fundus features, fluorescein angiography, course, management, histologic characteristics, and differential diagnosis of this rare entity in detail.^{1,3}

Involvement of the retina and central nervous system by a cavernous hemangioma was described by Weskamp and Cotlier in 1940.⁴ Their patient, a 17-year-old girl, had two capillary malformations of the occipital scalp and convulsions at the age of 12 years. Radiologic evidence of intracranial calcification was obtained, and a cavernous hemangioma was extirpated from the pre-Rolandic region. Gass described a patient with seizures, hemangioma of the retina, and cutaneous angiomas.² This patient's father had had epilepsy and died of an intracranial hemorrhage. Cavernous hemangioma of the midbrain, pons, and cerebellum were noted at necropsy.

It has been exceedingly difficult to establish a definitive diagnosis of intracranial cavernous hemangiomas ante mortem. As recently as 1974, Roberson et al described the "cryptic" nature of these lesions.⁵ These authors concluded that autopsy-proved cavernous hemangiomas had eluded angiographic demonstration ante mortem. As with our patient, even bone subtraction studies were of little benefit. In our pedigree, the proband uniquely had a total right third nerve palsy, but further statements regarding this ophthalmoplegia would be speculative. It may have been unrelated to the retinal hamartoma. The left temporoparietal findings were inconclusive and could represent a second lesion.

Colvard et al recently described retinal cavernous hemangioma in two patients.⁶ One individual was a 48-year-old man with cutaneous angiomas, cavernous hemangioma of the right retina, and paresthesias in the right arm and leg, as well as paresis of the left sixth and seventh cranial nerves. The intracranial process was localized to the left pons and the lemniscus medialis. A second patient was a 19-year-old man with congenital cardiovascular anomalies. In this second patient, the cavernous hemangioma of the retina was observed over a five-year period, and sclerosis of some of the larger saccules as well as minimal extravasation of fluorescein from the hamartoma were among the notable features.

A variety of cutaneous lesions have been described in association with retinal cavernous hemangioma. Mildner described a 14-year-old girl with cavernous hemangioma of the retina.⁷ She had a cavernous hemangioma removed from her chest early in life. Gass relates that small cutaneous angiomatous hamartomas are rather common, and thus, their presence in patients with cavernous hemangioma of the retina may be a chance finding.³ Retinal cavernous hemangiomas have also been associated with angioma serpiginosum, a dermatologic entity demonstrating progressive, widespread dilation of the subpapillary venous plexuses.⁸ These skin lesions are progressive from the first year of life throughout adolescence and are associated with motor and sensory loss due to vascular involvement of peripheral nerves. This entity further emphasizes the wide spectrum of cutaneous abnormalities that may be associated with retinovascular hamartomas.

To the best of our knowledge, this

article contains only the fourth account of bilateral involvement by cavernous hemangioma of the retina. The pedigree suggests a hereditary syndrome with highly variable penetrance and expressivity.

The phakomatoses are a group of multisystem hamartomas with the potential for ocular involvement. Sturge-Weber syndrome and von Hippel-Lindau disease also involve structures of mesodermal origin. In the former, cavernous hemangiomas of the choroid are associated with telangiectasias of the skin in the distribution of the trigeminal nerve, as well as pial hemangiomas. In the latter, cerebellar hemangiomas are associated with retinal capillary hemangiomas. These hemangiomas demonstrate that multisystem hamartomas need not be of the same cell type although they arise from the same embryologic cell layer.

Evidence is accumulating for the association of retinal cavernous hemangiomas with intracranial cavernous hemangiomas and cutaneous vascular hamartomas of a somewhat variable nature. This pedigree prompts careful continued examination of all family members, and while the prognosis for the affected eye appears to be generally good, the clinician should be aware that the patient or a member of the patient's family may harbor a threatening intracranial vascular lesion.

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