Familial Cavernous Hemangioma
An Expanding Ocular Spectrum

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Objective: To describe the clinical and genetic findings in a family with multiple cases of cavernous hemangiomas.

Design: Investigational clinical and genetic study in which 3 generations of a family consisting of 12 members were screened with magnetic resonance brain imaging, dilated ophthalmoscopic examination, and cutaneous survey coupled with linkage analysis to determine affected individuals and to better define manifestations of this neuro-oculo-cutaneous syndrome.

Results: The proband had multiple cerebral cavernous hemangiomas and a choroidal hemangioma. Her son was found to harbor a retinal cavernous hemangioma. The proband’s sister manifested a cerebral cavernous hemangioma, cutaneous hemangiomas, and a presumed choroidal hemangioma; her daughter demonstrated radiological findings suggestive of a cerebral cavernous hemangio. The father of the proband demonstrated multiple, cutaneous hemangiomas. The remaining family members were free of lesions. The 7q locus could not be excluded as harboring the causative gene.

Conclusions: This family may have a dominantly inherited neuro-oculo-cutaneous condition of cavernous hemangiomas with variable expressivity. The presence of choroidal hemangiomas in this phacomatosis has not been described previously to our knowledge.

Clinical Relevance: The presence of either retinal cavernous or choroidal hemangioma should alert the physician to search for features suggestive of systemic and familial involvement; either lesion may constitute the ocular component of the neuro-oculo-cutaneous phacomatosis, sometimes referred to as cavernoma multiplex.

Arch Ophthalmol. 2000;118:969-973

THE NEURO-Oculo-cutaneous syndrome of hemangiomas consisting of cavernous hemangiomas of the brain, retina, and skin was first convincingly documented in the South American literature and was subsequently reported by others. Members of an affected family may harbor any or all of these features.

Ocular manifestations of this phacomatosis have been exclusively retinal cavernous hemangiomas, a relatively rare entity consisting of an isolated cluster of retinal saccular aneurysms. First described in 1934 by Niccol and Moore, retinal cavernous hemangiomas are rarely associated with exudate but may occasionally bleed and are recognized by the finding of erythrocyte layering on fluorescein angiography. We describe a family of 3 generations with the various vascular malformations typical of the syndrome. In addition, there was the unique finding of choroidal cavernous hemangiomas.

CLINICAL FINDINGS

The pedigree is illustrated in Figure 1. The proband (II:3) was seen because of a 2-week history of left-sided numbness, weakness, and ataxia at age 31 years. Magnetic resonance imaging (MRI) of the brain revealed heterogeneous signal intensities characteristic of a right parietal cavernous hemangioma. An associated rim of intracerebral hemorrhage was present (Figure 2, A). Other cerebral cavernous hemangiomas were noted. The parietal lesion was removed, and the diagnosis of cavernous hemangioma was confirmed by histopathologic examination. Results of a cutaneous screening were unremarkable.

The proband was aware of gradually worsening vision of the right eye during the course of several years. Vi-
ual acuity was 20/200 OD and 20/15 OS. There was an elevated inferotemporal, yellow-red choroidal mass in the posterior pole with an overlying serous retinal detachment (Figure 2, B). Fluorescein angiography corroborated these findings and demonstrated early hyperfluorescence and marked late leakage (Figure 2, C and D). Ultrasonography showed a dome-shaped mass with basal dimensions of 4.3 \times 4.4 \text{ mm} and a height of 1.8 mm; moderate to high internal reflectivity, no choroidal excavation, and low blood flow were also noted (Figure 2, E). A diagnosis of choroidal hemangioma was made.

The proband’s son (III:3) was a healthy 10-year-old with no history of headaches or seizures. An MRI of the brain demonstrated suspicious T2-weighted hypointense signals in the periventricular white matter bilaterally that were suggestive of cavernous hemangiomas. A flat, cutaneous, serpiginouslike angioma on the nape of his neck was present; there was no blanching with pressure. Findings from ophthalmoscopic examination of the right eye revealed an isolated, superonasal, midperipheral cluster of retinal saccular aneurysms with the classic appearance of a retinal cavernous hemangioma (Figure 3).

The proband’s sister (II:1) had a right occipital cavernous hemangioma detected by MRI obtained after the onset of a grand mal seizure at age 38 years. The lesion was removed, and the diagnosis was confirmed by histopathologic examination. She had been aware of 2 cutaneous hemangiomas (<2.5 cm in diameter) on her right arm from early life that had not changed. They were red, did not blanch on pressure, and were clinically consistent with a mature, cavernous hemangioma. She denied any ocular complaints, but a well-circumscribed, flat choroidal lesion containing many large vascular channels was noted in the superonasal quadrant of the right fundus (Figure 4, A). Fluorescein angiography demonstrated minimal hyperfluorescence early with diffuse, late staining (Figure 4, B). Results of indocyanine green angiography and ultrasonography were noncontributory. Although other diagnostic possibilities, such as an amelanotic nevus, could not be conclusively ruled out, the lesion was most consistent with a choroidal hemangioma despite the atypical yellow color.16

The proband’s niece (III:1) noted a long history of migraine headaches and peripheral neuroesthesia. An MRI demonstrated a high suspicion for the presence of a cerebral cavernous hemangioma. Findings from a cutaneous survey and ophthalmoscopic examination were within normal limits.

The proband’s father (I:1) was a healthy, asymptomatic 66-year-old with no notable medical history. Imaging studies of the brain were deferred. The patient had a birthmark over the right buttock that had remained unchanged (Figure 5). The purplish papule was minimally elevated measuring 5 \times 5 \text{ cm}, did not blanch on compression, and was typical of a mature cavernous hemangioma. A similar lesion was removed from the facial region and found to be consistent with a cutaneous hemangioma on histopathologic examination. Lesions were also present under the tongue and on the skin of the neck. Findings from ocular examination revealed the presence of 2 subtle, solitary microaneurysms in the peripheral right fundus that were not appreciated by photography and may represent an incidental finding. The remainder of the ophthalmological examination was within normal limits.
The remaining members of the family were carefully surveyed by detailed history, cutaneous screening, and dilated ophthalmoscopy; none were found to harbor any features of this syndrome, and therefore, no further investigations were performed. Results of haplotype analysis confirmed affected and unaffected members.

Peripheral blood was obtained, and genomic DNA was extracted with the Nucleon II extraction kit (Scotlab Bioscience Ltd, Glasgow, Scotland). Genomic DNA was amplified with primers specifically corresponding to the polymorphic microsatellite poly-CA regions; these markers17-19 are shown in Figure 1. Polymerase chain reaction products were separated by nondenaturing polyacrylamide gel electrophoresis (Protogel; National Diagnostics, Atlanta, Ga) and visualized under UV illumination after staining with ethidium bromide. Alleles were assigned to individuals, and calculation of lod scores was performed with the Cyrillic and Fastlink software programs (Cherwell Scientific, Oxford, England). A maximal lod score of 1.81 was obtained with marker D7S527 at q=0 (Table). The lod score was low because of the small pedigree, but approximately 50 other microsatellite markers throughout the genome were tested for linkage in this family, and all yielded negative lod scores. There was segregation of the disease haplotype with the abnormal phenotype across a 29.4-centiMorgan region of 7q, which cannot be ruled out as the location for the causative mutated gene in this family.

**COMMENT**

The presence of cerebral, retinal, and cutaneous cavernous hemangiomas in 3 generations of this family is consistent with the diagnosis of an autosomal dominant neuro-oculo-cutaneous syndrome. Our patients had none
of the systemic characteristics of those conditions associated with choroidal hemangioma such as Sturge-Weber or Klippel-Trenaunay-Weber syndrome. Furthermore, they had circumscribed choroidal hemangiomas that are unlike the diffuse hemangiomas described in these conditions.

The phenotype is more consistent with the autosomal dominant phacomatosis, consisting of cerebral, retinal, and cutaneous cavernous hemangiomas and alternatively referred to as cavernoma multiplex. In this family, the nature of the lesions is characteristic of the disorder on clinical as well as histological grounds. To our knowledge, choroidal hemangiomas, the diagnosis of which was definite in one member of this family but equivocal in another, have not been reported in this syndrome. This is surprising given the similar histopathologic nature of these lesions; most choroidal hemangiomas contain cavernous elements histopathologically. Moreover, cavernous hemangiomas are known to affect multiple tissues in a family, including different areas of the central nervous system, the skin, and the liver. Even histologically different cerebral vascular anomalies may be present within one family; the coexistence of a cerebral cavernous malformation and an arteriovenous malformation has been reported in a single family. The causative gene has been localized to the region 7q11-q22. Approximately 50% of patients with a cerebral cavernous hemangioma have this hereditary syndrome and usually have multifocal, intracerebral involvement. The gene has yet to be identified, and good candidate genes are not known to exist in this region. The 7q locus has been excluded in 2 Hispanic families that had the typical features of this syndrome. In this family, we could not exclude the 7q locus as the region harboring the causative gene. The presence of choroidal hemangiomas in this syndrome may reflect variable expression of the disorder. In surveys of families with this condition, it would be wise to seek choroidal hemangiomas since there are consequent therapeutic implications.

Accepted for publication August 2, 1999.

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REFERENCES


A look at the past . . .

The primary step in the intracapsular operation is the subluxation of the lens by rupture of the suspensory ligament. The facility of this rupture depends on the state of the suspensory ligament and of the capsule of the lens, and it may be said that the success of the intracapsular extraction rests on 2 factors: the capsule of the lens and the zonular fibers and on their relation.