# **Familial Cavernous Angiomas:** Natural History and Genetic Study Over a 5-Year Period

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In a kindred of 122 individuals we found 5 individuals with cerebral vascular malformation, 3 representing typical cavernous angiomas. The condition was inherited as an autosomal dominant trait with variable expressivity. Forty-three relatives were examined prospectively by cranial computed tomography (CCT) and lesions were found in 15; 7 were followed prospectively with CCT scans for 5 years. Angiography in 5 of these cases failed to demonstrate the lesion. In 3 patients with previously normal CCT scans a change in blood volume or membrane permeability allowed visualization of the lesion on contrast scans. In 2 individuals, both parents of affected children, a normal CCT scan was found. This emphasizes the limitations of CCT in detecting this disorder. Biochemical and red blood cell immunological genetic linkage studies were done in 36 persons. No linkage was found with any of the markers. The natural history of this disorder, characterized by marked clinical and radiographic variation in site of lesion, and the timing and severity of intracranial hemorrhage, make it a useful model for investigating contributing factors and consequences of intracranial hemorrhage in general. For atrisk and affected patients early and sequential CCTs are necessary. Familial cavernous angioma should be included in the differential diagnosis of all young persons presenting with cerebrovascular impairment, seizures, intracranial calcifications or hemorrhage.

Key words: tomography, X-ray computed, arteriovenous malformations, genetics, medical, brain, contrast media, abnormality, autosomal dominant inheritance of familial cavernous angiomas

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#### INTRODUCTION

Vascular anomalies of the brain may be classified into four groups: arteriovenous anomalies, venous anomalies, capillary telangiectases, and cavernous angiomas [Russell, 1971]. The first three types appear to be sporadic conditions. Familial cavernous angiomas (FCA) of the central nervous system can cause headaches, seizures, and focal neurologic deficits due to hemorrhage. To date, FCA has been reportd in 24 persons in 6 families [Bicknell, 1978; Clark, 1970; Kidd, 1947; Michael, 1936; Kufs, 1928]. Our description of the present family shows: cranial computed tomography (CCT) is a sensitive but not infallible means of recognizing the presence of, and minimal changes in, even very small lesions; radiographic changes do not always reflect clinical changes; and some patients with the mutant gene may not express it at all. This family also emphasizes the significance of small, angiographically occult vascular malformations, which have been postulated as the cause of nontraumatic, nonhypertensive, spontaneous cerebral hemorrhage [Margolis, 1951]. Such lesions may be more common than has been generally supposed [Kramer, 1977].

#### MATERIALS AND METHODS

Family R was ascertained through patient III-2. History and physical examination data, and results of CCT scans and of genetic linkage analyses were tabulated and are reflected in Figure 1. Clinical and radiographic data were collected and correlated by one person (L.A.H.). CCT scans were performed without contrast medium in 43 adults and adolescents and again after intravenous injection of 80 gm of Iodine (in the form of diatriazoate meglumine, U.S.P., 30%) in 29 of them. An EMI 1010 headscanner was used at an 80-sec scan rate. Scans were performed several times over a 5-year period on 7 patients. CCT scans from other hospitals were obtained in individuals IV-15 and IV-17.

In 36 subjects 2 or more ml of saliva and 10 ml of venous blood (anticoagulated with citrate-dextrose solution) were collected for genetic marker studies. These samples were typed for the genetic markers acid phosphatase (AP), glucose-6-phosphate dehydrogenase (G6PD), 6-phosphogluconate dehydrogenase (6PGD), adenylate kinase (AK), adenosine deaminase (ADA), peptidases (Pep) A, C, and D, haptoglobin (Hp), phosphoglucomutase 1 (PGM1), esterase D (ESD), glyoxalase 1 (GLO1), glutamic-pyruvic transaminase (GPT1), the ABO, Rhesus, MNSs, Kell, Duffy, Lewis, P and Kidd red blood cell antigen groups, the Gm and Km  $\gamma$ -globulin types and secretor phenotype, as previously described [Ferrell et al, 1978]. Linkage analysis using informative loci was carried out by the maxium likelihood method (LIPED) [Ott, 1974].

Histologic sections of cerebral lesions in Individuals III-2, IV-6, III-15 were examined by one author (P.O.). An autopsy report in Individual IV-38, and a surgical report in Individual IV-15 were obtained.

#### **Reports of Family and Patients**

This large family (Fig. 1) of Mexican – American origin had no unusual or excessive health problems except for those due to the cavernous angiomas of the brain.





Individual III-2. The propositus was 52 years old. At 21 years, after 2 years of intermittent "blackout spells" and episodes of severe frontal headaches, anticonvulsant medication was begun for treatment of major motor seizures. At 26, during hospitalization for status epilepticus and subarachnoid hemorrhage, skull radiographs demonstrated intracerebral calcifications in the left temporal and right occipital lobes. Results of carotid angiography and pneumoencephalography were normal except for these calcifications and slight enlargment of the lateral ventricles. The patient continued his medication and functioned well for 23 years. At 49, he was admitted because of sudden aphasia, weakness of the right limbs, and recurrence of grand mal seizures. Results of cerebral angiography and pneumoencephalography were again unremarkable, except for increased size of the aforementioned foci of intracerebral calcification, and ventricular enlargment. A radionuclide brain scan showed increased tracer uptake at the calcified lesions within the left temporal lobe and right occipital lobe. CCT after rapid intravenous infusion of contrast medium demonstrated the previously identified calcified lesions and an additional calcified lesion adjacent to the body of the left lateral ventricle. Moreover, two smaller zones of dense enhancement were seen, one at the right parietal convexity, and another within the white matter adjacent to the anterior horn of the right lateral ventricle. During that hospitalization, the left temporal calcified lesion was resected and found to represent a cavernous angioma, with evidence of previous adjacent hemorrhage. After the operation, aphasia lessened but right hemiparesis persisted. Postoperative CCT (Fig. 2A) showed the effects of resection of the left temporal calcified angioma and no change in the other cerebral lesions.

At 51, he suddenly developed a right hemiplegia, with complete aphasia; a CCT scan demonstrated a large hematoma in the left centrum semiovale adjacent to the calcified lesion at the left lateral ventricular margin. Other lesions were unchanged. This hematoma and the small calcified cavernous angioma from which it arose were removed. Twelve weeks after this operation, he returned to the hospital for elective removal of the large calcified right occipital cavernous angioma. Before this operation, CCT demonstrated a new, 1 cm broad right temporal hematoma, which had been clinically silent. Four weeks later CCT showed innumerable new contrastenhanced lesions in areas of the brain previously thought to be uninvolved (Fig. 2B). No clinical manifestations of these new lesions were apparent. The small hematoma at the right temporal lobe had resolved and was replaced by a focus of contrast enhancement. Fourteen months later, CCT showed faint calcification in this area and another new asymptomatic hemorrhage at a cerebral convexity lesion site. There was no change at the other larger, densely calcified lesions. An ophthalmologic examination demonstrated no evidence of retinal angiomas. CCT 6 months later showed hemorrhage adjacent to the left convexity and right temporal lesions. He has become progressively demented over this time period.

Individual IV-6. The daughter of the propositus was 30 years old. At 9 years, she developed transient left hemiplegia and diplopia, and had a major motor seizure. At 27 years, she began to take diphenylhydantoin for occasional nocturnal seizures. Two years later focal seizures involving the left upper limb began to occur during waking hours, and calcification in the right frontal lobe was identified on skull radiographs. Cerebral angiography at that time was otherwise normal; but CCT demonstrated three large, partially calcified, discrete contrast-enhanced zones. The largest lesion was within the inferior aspect of the right frontal lobe. A small in-



Fig. 2. Contrast CCT of Individual III-2. (A) Scan following removal of a cavernous angioma from the left temporal area. Arrow marks a calcified lesion in the posterior pole of the right cerebral hemisphere. (B) Scan 12 weeks later at the same level, demonstrating two additional zones of enhancement while the patient developed no new symptoms. Note the absence of change in the calcified lesion. Scans demonstrate strikingly atrophic changes which occurred over the 5-year period of observation of this study and presumably represent cumulative effects of small hemorrhages.

tracerebral lesion was identified at the superior convexity of the posterior right frontal lobe. A third lesion was located in the pons. Four months later, she experienced transient weakness of the left upper limb, and CCT demonstrated a large hemorrhage surrounding the superior frontal angioma. Thirteen months after this, when the patient was asymptomatic and the neurological examination normal, a repeat CCT scan showed a new, recent hemorrhage surrounding the inferior frontal lobe lesion (Fig. 3), and a cerebral angiogram showed only the large intracerebral avascular hematoma mass within the right frontal lobe, without demonstrating an arteriovenous malformation per se. This frontal lobe hematoma was excised, in company with a partially calcified cavernous angioma, the specimen demonstrated acute and chronic hemorrhage. After operation, CCT showed no change in the remaining lesions which had remained clinically quiescent.

**Individual II-3.** The 71-year-old mother of the propositus had senile dementia, but no other neurological deficits. Serial CCT scans demonstrated cerebral atrophy and a partially calcified, contrast-enhanced zone in the white matter adjacent to the undeformed left frontal horn. A radionuclide brain scan demonstrated abnormal tracer uptake in this area.

Individual II-4. The brother of II-3 died at 58 years of a "cerebrovascular accident." We think he was affected because he had two sons, a granddaughter, and a great grandson known to be affected.

Individual II-5. The 80-year-old sister of the previous two individuals had no history of headaches, seizures, or intracerebral hemorrhage. Skull radiographs and CCT demonstrated a 1-cm calcified right frontal lesion. She died 2 years later.

Individual III-1. The 53-year-old sister of the propositus had CCT scans (before and after infusion of contrast material) which were normal. This was unexpected because she is an obligate heterozygote for the mutant gene with an affected parent, affected siblings, and three affected children. Her husband is nonconsanguineous.

**Individual IV-2.** The 34-year-old daughter of Individual III-1 had focal seizures involving the left leg. CCT demonstrated a contrast enhanced zone adjacent to the right lateral aspect of the falx cerebri within the parietal lobe.

Individual IV-4. The 25-year-old brother of the previous woman was asymptomatic. CCT demonstrated three small discrete nodules indicating cavernous angiomas in the superior convexity of the white matter of the right cerebral hemisphere.

Individual IV-5. The 22-year-old sister of the previous man was asymptomatic. However, CCT demonstrated a small, discrete, high density nodule in the white matter along the lateral aspect of the left occipital horn. There was minimal density enhancement of this lesion after infusion of contrast medium.

Individual III-4. The 44-year-old sister of the propositus denied any symptoms or neurological deficits. She refused to be scanned. Suspicion that she bears the mutant gene stems from the findings in her son.

Individual IV-11. The son of the previous woman died at 22 years. Autopsy revealed intracerebral hemorrhage originally ascribed to an unexplained fall.

Individual III-5. The 54-year-old sister to the propositus had a normal CCT scan and was asymptomatic. She is included because of two affected children from a nonconsanguineous marriage.



Fig. 3. Contrast CCT of Individual IV-6 showing three phases of hemorrhage surrounding right frontal angioma. The vertical arrow marks calcification caused by earlier hemorrhage and the horizontal arrow marks resolving subacute hemorrhage. Acute hemorrhage has produced the lobulated high density area at the medial aspect of the hemorrhagic zone.

Individual IV-15. The 15-year-old son of previous woman had had sudden onset of left sided numbness. A CCT scan showed large right hemispheric hemorrhage. Angiography showed mass effect and several questionably abnormal vessels. At surgery a large hematoma surrounded by gliosis was discovered. The pathology specimen showed cavernous angioma in right parietal area. Postoperatively he had a left hemiparesis.

**Individual IV-17.** The 21-year-old brother of the previous individual has a calcified lesion in the right parietal area on CT scans which did not enhance on the contrast study. He is on medication for a seizure disorder.

Individual III-7. The 46 year-old sister of the propositus developed focal seizures involving the right side of her body at 10 years. At 28 years calcification was identified in the superior parietal convexity of the left cerebral hemisphere. Carotid angiograms were normal. CCT at 42 years showed a large, partially calcified lesion at the superior convexity and parasaggital aspect of the left parietal lobe. Results of repeat CCT 15 and 39 months later were unchanged.

Individual III-8. The 42-year-old brother of the propositus has had intermittent severe headaches for 20 years. His neurological status was normal. CCT showed a partially calcified contrast-enhanced lesion within the corpus callosum. A small calcification in the central white matter of the left cerebral lobe was also identified. Repeat CCT after an episode of transient loss of strength in the left hand, and again 2 years later, showed no change in the lesions.

Individual IV-22. The 20-year-old daughter of the previous man was asymptomatic. CCT demonstrated a small calcified nodule in the white matter of the left parietal convexity which did not enhance after contrast was administered. Eighteen months later she experienced numbress of the right arm and a repeat scan demonstrated a hematoma surrounding the calcified focus. In addition, linear enhancement was observed in the right calcarine cortex which had been previously normal.

**Individual IV-24.** The brother of the previous person died at 6 years, due to accidental injuries. We think he had FCA because of a previous history of frequent and severe headaches.

**Individual III-12.** The first cousin of the propositus died suddenly at 52 years from an unexplained fall. No cause of death was apparent at autopsy. We think that his death may have been due to FCA since his daughter was affected.

Individual IV-38. The 32-year-old daughter of the previous person had two episodes of numbness of her left hand at 19 years. Two months later, she developed numbness of the left side of the body. Paralysis of the left limbs and face ensued. Angiography showed only mass effect. A right parietal lobe hematoma and vascular anomaly consisting of dilated venous channels was resected. At 31, CCT showed postoperative changes at the superior right parietal cerebral convexity and focal calcification in cortex of the left frontal lobe. A circumscribed area of contrast enhancement was identified surrounding this calcification (Fig. 4).

**Individual V-21.** The 15-year-old son of the previous woman was asymptomatic. CCT showed a large focal zone of calcification in the right parietal lobe cortex and enhancement on repeat scans after infusion of iodinated contrast medium.

Individual III-15. The 28-year-old first cousin of the propositus began to have choreiform movements of his left arm at 7 years. Subsequently, involuntary movements involved the opposite upper limb, neck, and facial muscles. Serial noncontrast CT scans were degraded by the involuntary movements but showed high density zones in the head of both caudate nuclei and the adjacent internal capsules which did not change. A zone of cerebral destruction was seen in the right temporal cortex. Autopsy demonstrated four 1- to 3-mm angiomas in the cerebellum and cerebral hemispheres with a large area of destruction in the right temporal cortex associated with an area of racemose dilated veins. Changes of Hallervorden--Spatz degeneration were found in the globus pallidus and substantia nigra accounting for the density zones seen at CT.



Fig. 4. CCT of Individual IV-38. (A) Precontrast CCT demonstrating a 4 mm calcification in the left frontal lobe (arrow). (B) Contrast CCT demonstrating enhancement of the cavernous angioma; this lesion, which resembles those seen in asymptomatic young adults, emphasizes both the small size and contrast enhancement of prehemorrhagic FCA lesions.

The maternal grandfather (I-1) of the propositus was not known to be affected although details of his medical history were not available. His wife (I-2) was not known to be affected but details about her health and death were not available. Many additional children, grandchildren, and great grandchildren from two other unrelated husbands were known not to have been affected.

### RESULTS

The genetic markers G6PD, AK, ADA, Pep A, C, and D, AP, GPT1, ESD and the ABO and Kidd blood groups were uninformative for linkage. Table I presents the results of LIPED analysis of data from informative loci. No significant positive lod score was observed between FCA and any of the test loci. Lack of association with chromosome 1 is suggested by the large negative lod scores for FY, PGM1, and RH. Individual phenotypes and gene frequencies used in this analysis are available upon request from R.E.F. (Gene Marker Laboratory, Graduate School of Biomedical Sciences, University of Texas Health Science Center, Texas Medical Center, Houston, TX 77030).

CCT was performed on 43 individuals. It demonstrated angiomas in 15, surgically and/or pathologically confirmed in 5 (III-2, IV-6, III-15, IV-15, and IV-38). Multiple cerebral lesions were seen in 6 patients (III-2, III-8, III-15, IV-4, IV-6 and IV-38) and solitary lesions in 7 patients (IV-2, IV-5, IV-22, IV-21, III-8, IV-15 and IV-17). In individuals II-3 and II-5, only single lesions were observed, but CCT quality was substandard. In two family members (III-1 and III-5), CCT of excellent technical quality, both with and without infusion of contrast medium, did not demonstrate cerebral angiomas, even though there were obligate heterozygotes with an affected parent, affected sibling, and affected children with nonconsanguineous husbands. Seven FCA patients were followed with CCT over 5 years. Their lesions showed three patterns of behavior: (1) In two (III-2 and IV-22), large new lesions appeared in areas which were previously normal on CCT scans. In III-2 existing angiomas remained unchanged after the new lesions appeared while in IV-22 a previously existing angioma bled. (2) In two persons (III-2 and IV-6), single lesions continued to bleed repeatedly over a period of months, while adjacent cerebral angiomas remained unchanged (Fig. 3). (3) In four patients (II-3, III-7, III-8 and III-15), the cerebral lesions remained quiescent, with no appreciable change in their CCT appearance while seizures and residual neurological deficits from previous cerebral hemorrhages persisted.

# DISCUSSION

# **Pathogenetic Considerations**

Familial instances of FCA provide an opportunity to study the natural history and pathogenesis of the condition. Six families with FCA have been described [Bicknell et al, 1978; Clark, 1970; Kidd and Cumings, 1947; Michael and Levin, 1936; Kufs, 1928]; all demonstrated autosomal dominant inheritance and severe clinical sequelae. This family is the first in whom CCT and genetic linkage studies were combined. Serial CCT scans over a 5-year period performed on seven affected family members demonstrated three patterns of disease progression. In most, lesions showed no change in the CCT appearance, although neurological deficits from previous hemorrhages persisted. Or, a single lesion bled repeatedly while adjacent foci remained quiescent, implicating a local aggravating factor. A third pattern in-

Locus 1	Locus 2	ź	$\hat{ heta}$	z (0.05)	z (0.1)	z (0.2)	z (0.3)	z (0.4)
FCA	FY	0	0.50	-2.16	-1.33	-0.58	-0.23	-0.05
FCA	GLO1	0	0.05	-1.63	-0.87	-0.26	-0.06	-0.00
FCA	GM	0	0.05	-1.46	-0.91	-0.41	-0.17	-0.05
FCA	HPA	0.56	0.15	0.38	0.53	0.53	0.36	0.14
FCA	КМ	0	0.50	-1.06	-0.64	-0.26	-0.09	-0.02
FCA	JK	0	0.50	-0.29	-0.22	-0.12	-0.04	-0.01
FCA	MNS	0	0.50	-2.35	-1.31	-0.46	-0.13	-0.22
FCA	Р	0	0.50	-0.91	-0.58	-0.26	-0.10	-0.02
FCA	PGD	0	0.50	-0.72	-0.44	-0.19	-0.07	-0.04
FCA	PGM1	0	0.50	-1.96	-1.16	-0.48	-0.18	-0.04
FCA	RH	0	0.50	-5.88	-3.87	-1.97	-0.97	-0.36
FCA	SE	0	0.50	-1.22	-0.73	-0.27	-0.08	-0.01

TABLE I. Lod Scores for Linkage Analysis of Familial Cavernous Angioma (FCA) With Serological and Biochemical Markers

Note: Gene symbols and format for presenting linkage data follow the convention of Keats et al [1979].

volved the appearance of small angioma(s). This pattern also implies that locally active factors play a role in determining the CCT visibility of the angiomas. Since the appearance of these new lesions reflects either a permanent alteration in membrane permeability to the contrast or an enlarged blood volume in the region of the malformation their appearance reflects a change in the lesion which seems to be abrupt and permanent.

Thus, factors in addition to the effect of the mutant gene may be major determinants of clinical severity. These factors may include blood pressure, blood levels of metabolites, hormones or enzymes; or cell-cell interaction may be critical in limiting or enhancing the effect of the mutant gene at a given site. Our demonstration of the altered CCT visibility of FCA lesions in two individuals over a short time period in areas of brain previously considered normal on high quality CCT scans (Fig. 2) is consistent with this interpretation [Russell, 1971; Voigt, 1976]. In these two individuals, hypertension and drugs were excluded and the reason for the change is not clear, but a factor elaborated locally or transported systematically may have affected adversely the abnormal capillary vessels. We have previously suggested that factors extrinsic to the mutant gene are important in the pathogenesis of Von Recklinghausen neurofibromatosis and other autosomal dominant disorders [Riccardi, 1979, a, b]. For example, in persons heterozygous for the familial hypercholesterolemia gene [Brown, 1976], the availability of lipoprotein-bound cholesterol in the blood seems to be an important local factor. In  $\alpha$ -1-antitrypsin (A1AT) deficiency the lack of serum-transported antitrypsin activity appears to determine the pulmonary manifestations of that disease.

Although the factors limiting or aggravating the local effects of the FCA gene are not identified, the cases presented here strongly implicate such factors. And since focal intracerebral hemorrhage is the critical clinical aspect of the FCA gene expression, recognition of local determinants and their influence on this expression may help our understanding of factors which contribute to intracerebral hemorrhage in general. Intracranial hemorrhage is a causally heterogeneous symptom: all stroke victims need to be evaluated to determine pathogenesis and cause. With stroke still a predominant cause of disability and death, all clues should be explored in a logical, complete manner in every patient with cerebrovascular compromise.

#### Management

Detection and follow up. FCA should be considered in evaluating all patients presenting with seizures, movement disorders, and signs of intracerebral bleeding, especially if there is an associated history of headache, onset at a young age, or similarly affected relatives. Moreover, an apparent stroke presenting in the fifth or sixth decade of life should not be presumed to result always from the more common mechanisms. For example, the development of symptoms due to cerebrovascular compromise in individuals II-3, II-4, II-5, III-1, III-2, III-4, and III-8 might have been attributed to arteriosclerotic cerebrovascular disease if complete radiologic and genetic data had not been collected and interpreted correctly. In younger persons other genetic causes of intracranial vascular compromise would also have to be considered, including Fabry disease, homocystinuria, sickle cell anemia, adult-onset polycystic kidney disease, and the Ehler-Danlos syndrome. The combination of seizures and intracranial calcifications, as in individuals III-2 and III-7, should lead to FCA evaluation and differentiation from tuberous sclerosis and Albright hereditary osteodystrophy. Angiomas of fundi (not seen in our patients) suggest the diagnosis of "cavernous hemangiomas of the retina and optic disc," which also may be inherited [Lewis, 1975]. Whether ocular involvement defines a separate entity is unclear.

The vascular anomaly produced by the FCA mutation has received little attention in the past because individual lesions were difficult to detect on routine angiograms, pneumoencephalograms or skull radiographs. To be detected by radionuclide scanning the lesion must have a diameter of at least 20 mm [Kawi, 1978]; with routine angiography only a subtle blush or unusual venous drainage pattern may be apparent [Kramer, 1977; Voigt, 1976; Kawi, 1978; Numaguchi, 1977; Bartlett, 1977; Jonutis, 1971; Segall, 1974] although selective, high dose, prolonged angiography may be useful [Numaguchi, 1979]. CCT scanning has dramatically improved the detection rate [Kramer, 1977; Bartlett, 1979] and confirmed the pathologists' suspicion that these lesions are *not* rare occurrences [Russell, 1971]. Moreover, as demonstrated here, CCT can be particularly useful in detecting bleeding lesions in functionally silent areas (eg, frontal lobe) and small nonhemorrhagic lesions not clinically apparent, though located in critical areas of the brain. The relatively high incidence of clinical symptoms and the ease of surgical removal underscore the importance of correctly diagnosing the lesion.

All first-degree relatives of a patient with FCA need to be evaluated with contrast-enhanced CCT scanning, even if apparently unaffected. Establishment of the diagnosis before the onset of symptoms (eg, Individuals III-1, III-4, IV-5, IV-21, and IV-22) would clarify a person's potential risks and the need for close clinical and CCT follow up, and rapid intervention in the event of minor symptoms. Moreover, such patients, as part of a prospective protocol, could be very helpful for obtaining data on pathogenetic mechanisms underlying the cause of spontaneous intracerebral hemorrhage. Whether pregnancy and delivery are additional risk factors is uncertain, although in our series they were not clearly so.

**Treatment.** Removal of a cerebral angioma may be relatively easy if the lesion, with or without associated hemorrhage, is accessible (Fig. 3). The high incidence of multiple lesions and the inability of CCT to detect *very* small lesions underscores the need for close postoperative follow up to detect clinically silent hemorrhage. However, the sensitivity of CCT is a mixed blessing. The detection of a small hemorrhage.

rhagic focus in an unsuspected person with headache or seizures could prompt exploratory surgery which might destroy adjacent normal brain in an attempt to locate the small lesion (Fig. 4). In addition, small lesions not detectable by present CCT capabilities may remain quiescent and long-term prognosis cannot always be predicted. In the event of operation, evaluation of the lesions with special histologic stains, electron microscopy and other research methods are to be encouraged to detect possible factors which caused the hemorrhage.

Genetic counseling. Genetic counseling should be made available to all family members. Based on early diagnosis using CCT scanning, an evidently affected person might avoid procreation or if a man, use artificial insemination by donor. Thorough study of other families would aid our understanding of the natural history of FCA, especially factors affecting its markedly variable expression. Presently, prenatal diagnosis is not possible. Negative studies do not preclude the presence of the mutant gene in at-risk individuals.

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