

Berry Aneurysms, Cirrhosis, Pulmonary Emphysema, and Bilateral Symmetrical Cerebral Calcifications: A New Syndrome

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Familial idiopathic nonarteriosclerotic cerebral calcification (FINCC) constitutes a rare but pathologically well defined disorder. Thus far, central nervous system symptoms and signs have been the only recorded expression of this disease. Autosomal dominant and autosomal recessive inheritance have both been postulated as cause. We describe three sibs who had symmetrical cerebral calcifications, but three also had cirrhosis and pulmonary emphysema; two had congenital cerebral aneurysms. All were male and of short stature; they also had delayed development and seizures, and two had other neurologic deficits. One sib died at age 3 years of hepatic failure and portal hypertension. Ruptured cerebral aneurysms led to the death of the other two boys at ages 8 and 13 years. The cerebral calcifications symmetrically involved the basal ganglia and thalami, the dentate nucleus, and the cortical and subcortical areas of the cerebrum. The liver was studied by sequential biopsies in two of the children and in all three by autopsy. Fatty degeneration and portal fibrosis preceded a periportal and micronodular cirrhosis. Severe bilateral pulmonary emphysema was present in one sib at age 12 years, whereas all three had bullae and cysts at autopsy. Ruptured left middle cerebral artery aneurysms were demonstrated in two sibs, and one also had aneurysms of the anterior and posterior communicating arteries. We conclude that in this family FINCC is a complex pleiotropic mendelian mutation, either of autosomal or X-linked recessive nature, whose basic pathogenesis remains unknown but may involve a metabolic defect. This form of FINCC may be a previously undescribed syndrome or a form of FINCC in which extraneural manifestations were previously overlooked.

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Dedicated to Dr. Enid F. Gilbert for her friendship and inspiring work over 30 years in fetal genetic pathology and in experimental teratology.

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TABLE I. Clinical History

Patient	Term	Motor	Development		Neurologic deficit	Seizures	Hepatomegaly	Clubbing	Death (years)	Cause
			Somatic	Mental						
1	+	Delayed walking	Short	Normal	—	+	+	+	3 ¹ / ₂	Sepsis
2	+	Delayed walking	Short	Retarded	Dysarthria, dysmetria, incoordination	+	+	+	8 ³ / ₂	Ruptured cerebral aneurysm
3 ^a	+	Delayed walking	Short	Superior	Dysarthria, dysmetria, incoordination	+	+	+	13 ³ / ₂	Ruptured cerebral aneurysm

^aProband. Patients 1 and 2 were deceased at the time of the initial evaluation of this family.

Key words: congenital cerebral aneurysms, familial idiopathic nonarteriosclerotic cerebral calcification, Fahr disease

INTRODUCTION

Familial idiopathic nonarteriosclerotic cerebral calcification (FINCC) constitutes a rare autosomal dominant or autosomal recessive disorder [Boller et al, 1977] with a well defined pathological pattern [Melchior et al, 1960; Löwenthal and Bruyn, 1968; Babbitt et al, 1969; Barwich, 1976; Constantinidis et al, 1978]. Thus far, central nervous system signs and symptoms have been the only recorded clinical expression of this disease [Löwenthal and Bruyn, 1968; Babbitt et al, 1969; Moskowitz et al, 1971; Kousseff, 1980; Harati et al, 1984].

We describe three brothers who, besides having symmetrical cerebral calcifications, also had hepatic and pulmonary disease; two had congenital cerebral aneurysms. We suggest that FINCC is a pleiotropic syndrome with diverse clinical manifestations. The extraneural components of FINCC have been either previously overlooked or incompletely expressed clinically. However, in this case, we may be dealing with a previously undescribed syndrome of FINCC with prominent extraneural manifestations.

CLINICAL HISTORY (TABLE I)

All three sibs were boys born at term; they were short. Height, weight, and head circumference of patients 1 and 3 were <3rd percentile. All three had seizures during infancy and delayed walking. Two had neurologic deficits including dysarthria, incoordination, and dysmetria; one child was mentally retarded. Clubbing of the digits (Fig. 1) and hepatomegaly were present in all three, and an increased anteroposterior chest diameter and radiologic signs of emphysema were evident in one boy. Patient 3 had an unusual



Fig. 1. Patient 3. Bilateral clubbing of the digits.



Fig. 2. Patient 3. Unusual facial appearance with hypertelorism, downward-slanting palpebral fissures, flat philtrum, and a vermilion border of the upper lip.

TABLE II. General Autopsy Findings

	Patient 1	Patient 2	Patient 3
Jaundice	+	-	-
Ascites	+	-	-
Peritonitis	+	-	-
Splenomegaly	+	+	+
Esophageal varices	+	+	+

facial appearance (Fig. 2). Results of an extensive work-up for hypoparathyroidism, α_1 -antitrypsin deficiency, and other metabolic causes of liver diseases were unremarkable. Hepatic failure constituted the main clinical problem in patient 1, who had increased bruisability, epistaxis, gastrointestinal bleeding, ascites, and pancytopenia. Peritonitis and acute bronchopneumonia following a portocaval shunt led to his death associated with disseminated intravascular coagulation and sepsis at age 3 years. The clinical presentations of the other two boys were predominantly those of ruptured cerebral aneurysms with headache, vomiting, hemiparesis, and coma. These two children died of subarachnoid hemorrhage and encephalomalacia. Parents are not consanguineous; family history is otherwise unremarkable. Reproductive history shows that the parents first two pregnancies ended in early spontaneous abortion. Their third, sixth, and seventh pregnancies resulted in the birth of patients 1, 2, and 3. The surviving sibs, who were products of their fourth and fifth pregnancies are now 23 years (male) and 20 years (female) old. Both sibs and their parents are asymptomatic but have refused evaluation.

PATHOLOGIC FINDINGS

The most important pathologic findings relate to the central nervous system, liver, and lungs. The remaining pertinent findings noted at autopsy are summarized in Table II.

Central Nervous System

Cerebral calcifications. The distribution of the calcifications is documented in Table III. The presence of calcifications was demonstrated antemortem by computerized tomography scan (Fig. 3) and confirmed by postmortem xerography (Fig. 4) in patient 3. Microscopically, the calcifications appeared as both vascular and nonvascular deposits. Both types of accumulations were present throughout the brain, midbrain, and cerebellum. Vessel-related calcifications were more evident in the white matter and nonvascular deposits in the grey matter. These deposits were basophilic, and staining reactions identified the presence of iron and calcium. Cellular reaction or neuronal changes were not

TABLE III. Central Nervous System Calcifications

Patient	Cerebrum				Cerebellum		
	Basal ganglia	Thalamus	Cortex	White matter	Cortex	White matter	Dentate nucleus
1	+	?	+	+	+	+	+
2	+	?	+	+	+	+	+
3	+	+	+	+	+	+	+

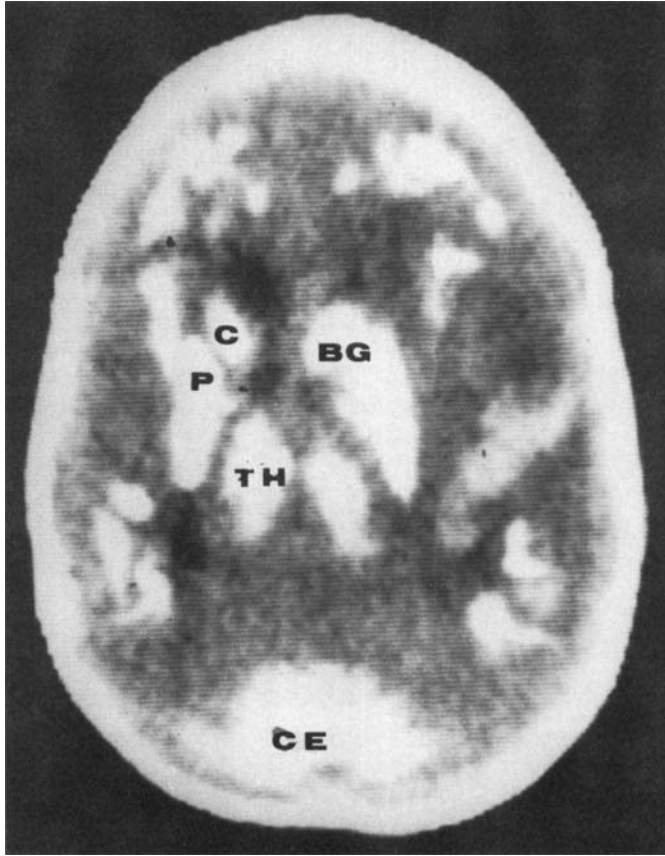


Fig. 3. Patient 3 at age 13 years. Computerized tomography depicting calcifications of basal ganglia (BG), thalamus (TH), and cerebellum (CE). C, caudate nucleus; P, putamen.

associated with these calcifications. The vessel-related deposits consisted of small granular spheres along the capillary wall, isolated or confluent, fine or coarse, with or without preservation of the vascular lumen (Fig. 5A). Calcifications were also seen in the media and adventitia of arterioles and small arteries of the cerebrum (Fig. 5B) and leptomeninges. The nonvascular calcifications were larger, of different sizes and shapes, and frequently confluent (Fig. 5C), with a homogeneous or lamellated appearance.

Cerebral aneurysms. Cerebral aneurysms were documented by angiography and by autopsy in patients 2 and 3. Aneurysms of the left middle cerebral artery had ruptured in both. Aneurysms of the right anterior and right posterior communicating arteries were noted by angiography and confirmed by autopsy in patient 3 (Fig. 6). Microscopic examination showed changes usually associated with berry aneurysms: thickened or focally absent internal elastic membrane, thickened or attenuated vascular wall with disorganized smooth muscle, and intimal fibrosis (Fig. 7A,B). The rupture site was composed of a blood clot with repair surrounded by recent and old hemorrhage. An intact larger artery adjacent to the ruptured aneurysm had a wavy, thickened, hyalinized internal elastic membrane and patchy subintimal fibrosis. No calcifications were seen in these vessels. Arteries of similar size but in different locations were unremarkable.

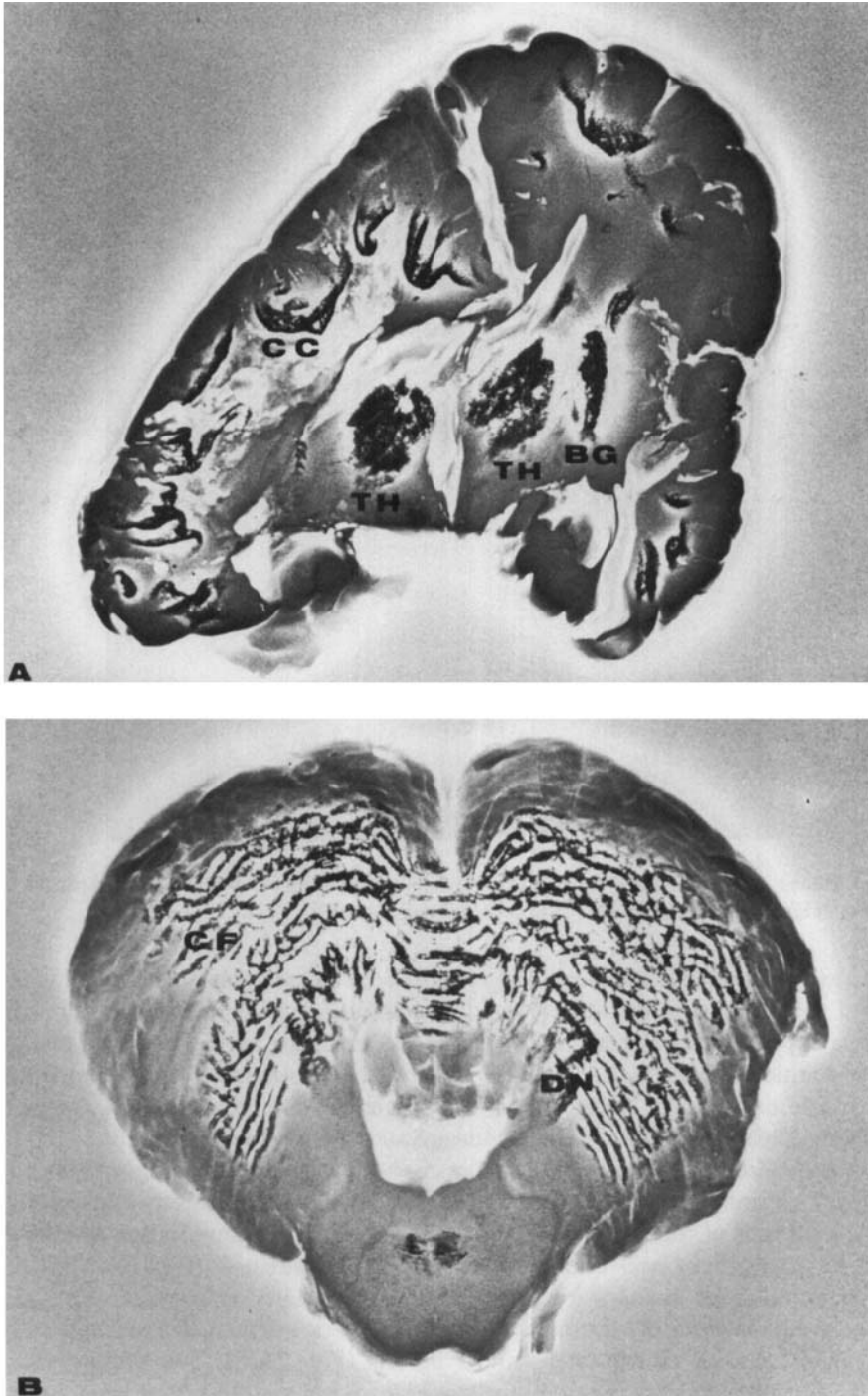


Fig. 4. Patient 3 at age 13 years. Xerography. **A:** Note bilateral calcifications of thalami (TH), basal ganglia (BG), and cerebral cortex (CC). **B:** Involvement of cerebellar folia (CF) and dentate nucleus (DN).

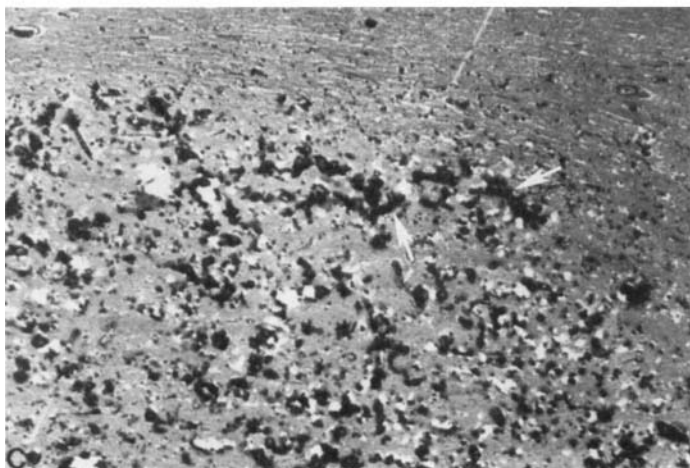
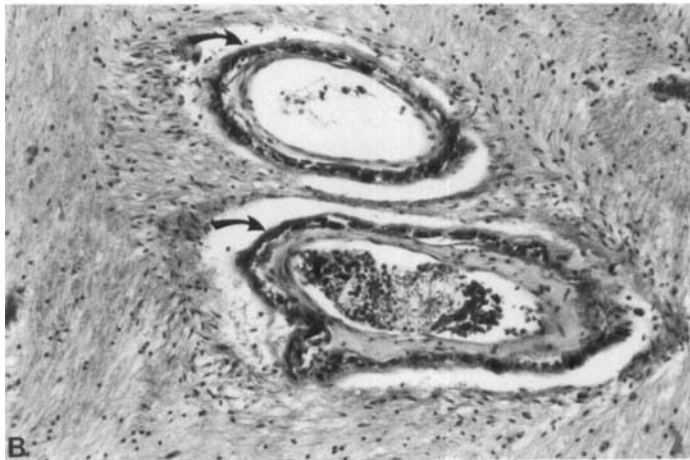
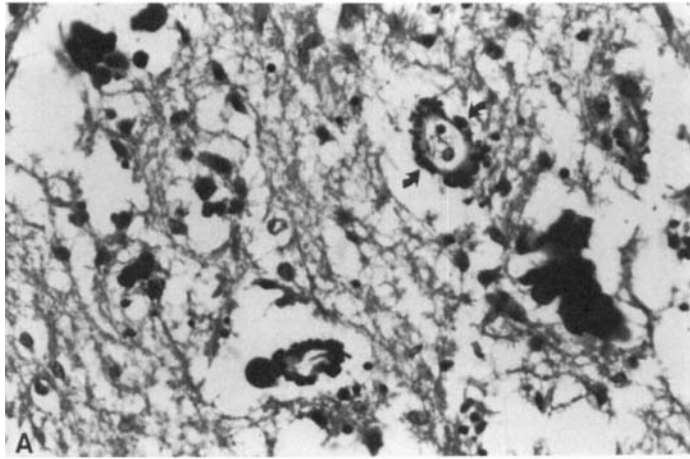


Fig. 5. Different microscopic patterns of cerebral calcifications. **A:** Fine granular calcifications adjacent to capillaries (arrows). Hematoxylin and eosin, $\times 200$. **B:** Calcifications of media and adventitia of small arteries (arrows). Hematoxylin and eosin, $\times 50$. **C:** Coarse interstitial calcifications (arrows). Hematoxylin and eosin $\times 200$.

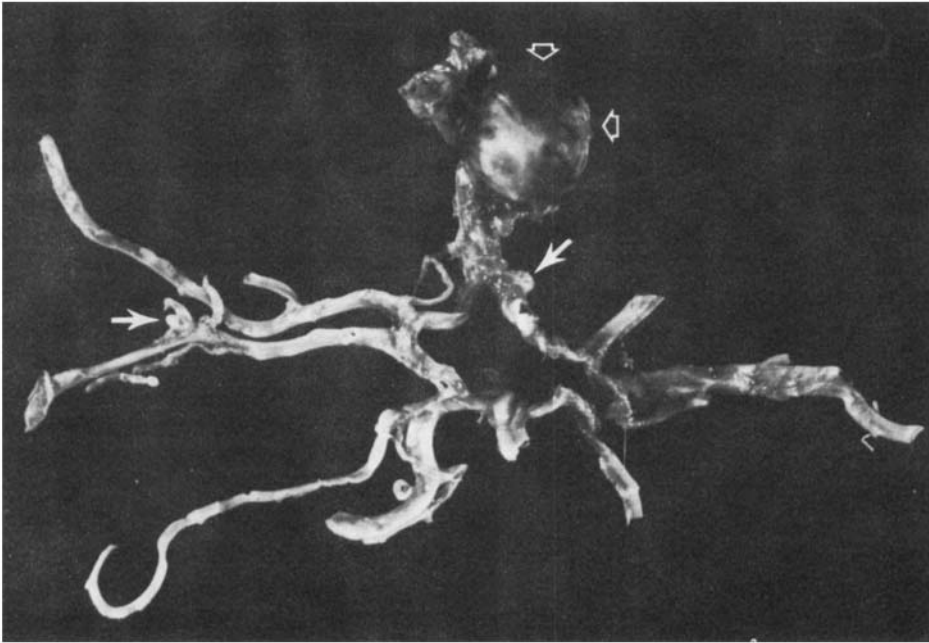


Fig. 6. Patient 3. Circle of Willis with multiple berry aneurysms (arrows). The largest is ruptured and involves the left middle cerebral artery (arrowheads).

Liver

Liver changes (Table IV) were studied by sequential liver biopsies in two of the children and in all three by autopsy. Macro- and microvesicular fatty degeneration predominantly of periportal hepatocytes constituted the only and earliest lobular change at age 6 months (Fig. 8A). The portal spaces were expanded by fibrosis and contained a moderate mononuclear cell infiltration and hemosiderin-laden macrophages. Portal bridging was present. Cirrhosis was apparent by 3 $\frac{1}{2}$ years with persistence of the fatty degeneration and portal mononuclear infiltration. The cirrhosis was predominantly periportal and micronodular. Minimal portal infiltration persisted, whereas the fatty degeneration was no longer apparent at 13 $\frac{1}{2}$ years (Fig. 8B,C). The rhodanine stain never demonstrated presence of any copper. α_1 -antitrypsin inclusions were not demonstrated by the D-PAS and immunoperoxidase stains. The interlobular bile ducts were intact. Peroxisomes were identified by electron microscopic examination.

Lung

Pulmonary emphysema with bleb and cyst formation was present in all patients. The emphysema was bilateral and more severe at the periphery (Fig. 9A,B). Cysts were focally associated with cholesterol granulomata and fibrosis, interpreted as a reaction to previous hemorrhage. Ruptured, richly vascularized interalveolar septae protruded into the cystically dilated air spaces.

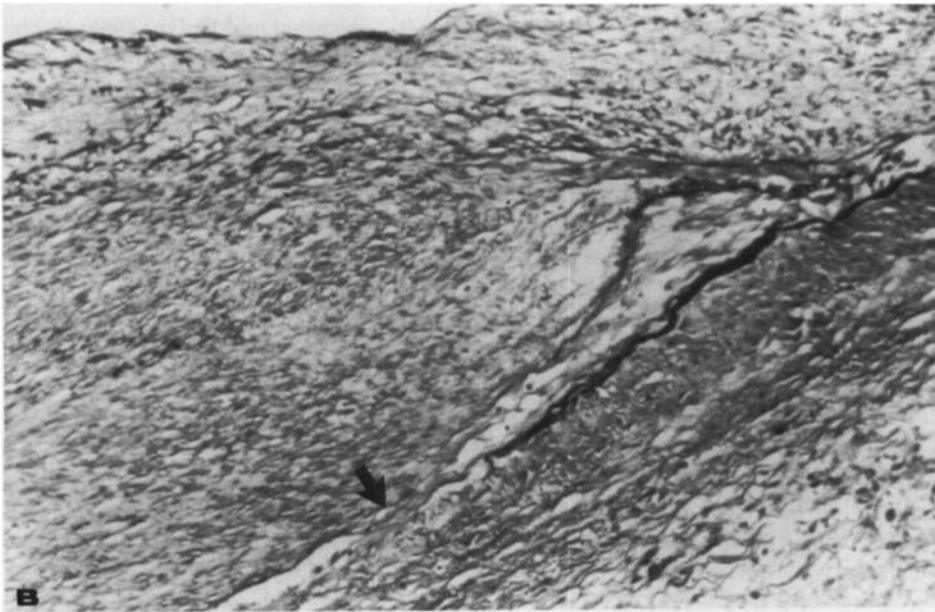
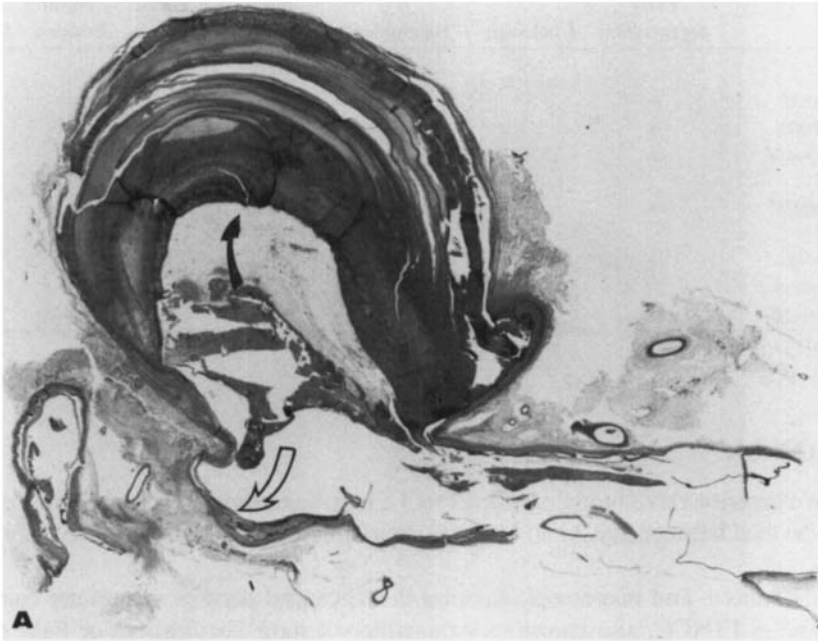


Fig. 7. Berry cerebral aneurysm. **A:** Whole mount. Note aneurysmatic dilatation with thrombus (solid arrow) and intact vessel wall (open arrow). Elastic Van Gieson stain, $\times 200$. **B:** Microscopic appearance characterized by intimal fibrosis and abnormal or absent internal elastic membrane (arrow). Elastic Van Gieson stain, $\times 200$.

TABLE IV. Hepatic Histology

Age	Fatty degeneration	Cholestasis	Hemosiderin	Portal infiltration	Portal fibrosis	Portal bridging	Cirrhosis
Patient 1							
6 months	+	-	Portal	+	+	+	-
3 ¹ / ₂ years	+	-	-	+	+	+	+
3 ¹⁰ / ₁₂ years ^a	+	+	-	+	+	+	+
Patient 2							
8 ³ / ₁₂ years ^a	+	-	-	-	+	+	+
Patient 3							
8 months	+	-	Portal	+	+	+	-
13 ³ / ₁₂ years	-	-	-	-	+	+	+
13 ³ / ₁₂ years ^a	-	+	-	+	+	+	+

^aAutopsy.

DISCUSSION

We describe three brothers with FINCC, hepatic cirrhosis, and pulmonary emphysema who died between age 3 and 13 years. In addition, berry aneurysms were present in two.

The macro- and microscopic findings in the central nervous system are consistent with those of FINCC, also known as strio-pallido-dentate calcifications or Fahr disease [Copeland et al, 1977]. In this entity, calcifications are present in the nucleus pallidus and dentate nucleus but may involve the entire basal ganglia, thalami, cortex, and subcortex of the cerebrum and cerebellum [Melchior et al, 1960; Löwenthal and Bruyn, 1968; Babbitt et al, 1969; Barwich, 1976; Constantinidis et al, 1978]. Hypoparathyroidism is present in two-thirds of these patients, whereas in the remaining familial cases the pathogenesis remains unknown [Hastings-James, 1970; Moskowitz et al, 1971]. The cerebral calcifications in our patients are most consistent with those described in the familial idiopathic group. In these patients, the pathogenesis of the cerebral calcifications also remains obscure. Local factors [Löwenthal and Bruyn, 1968; Schéda, 1970; Seth and Roy, 1972; Aicardi and Goutières, 1984] or more generalized metabolic defects [Dinkel, 1971] have been postulated. Growth retardation [Babbitt et al, 1969], seizures, mental deficit, and cerebral motor and cerebellar disorders [Moskowitz et al, 1971; Kousseff, 1980] usually became apparent after age 35 years but may be present in childhood [Moskowitz et al, 1971].

Our three patients all had idiopathic cirrhosis, and two had splenomegaly and esophageal varices as signs of portal hypertension. Why liver failure developed only in patient 1 is unclear. Cirrhosis was preceded by fatty degeneration and was well established by age 3 years. Fatty degeneration and cirrhosis have been described in two of four relatives with FINCC [Cockel et al, 1973], but pulmonary emphysema and cerebral aneurysms were not mentioned.

Patients 2 and 3 died of subarachnoid hemorrhage and encephalomalacia from ruptured berry aneurysms of the left middle cerebral artery. At autopsy, patient 3 had two additional aneurysms in the anterior and posterior communicating arteries. The microscopic pattern was similar to that described in patients with congenital aneurysms [Bolander et al, 1978; Rodin et al, 1982]. These autosomal lesions are rare in children, and associated findings, such as those in our patients, have not been reported previously [Rodin et al, 1982].

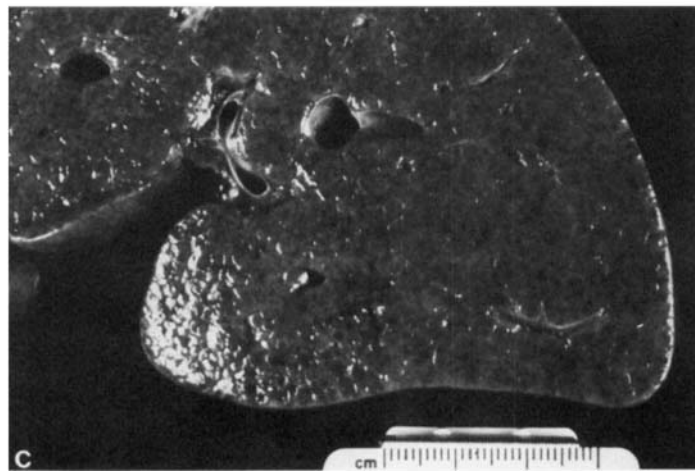
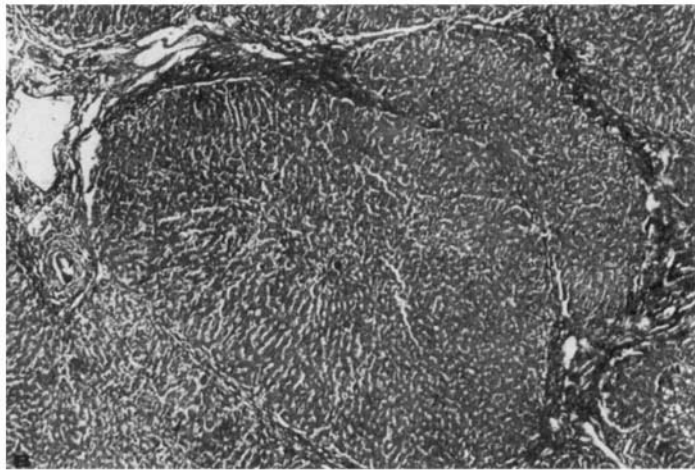
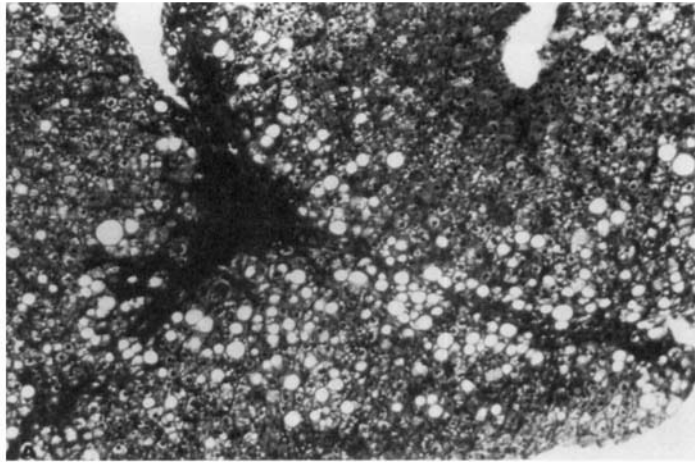


Fig. 8. Sequential hepatic changes of patient 3. **A:** Liver biopsy at age 18 months. Moderate fatty degeneration with portal fibrosis. Hematoxylin and eosin, $\times 200$. **B:** Liver biopsy at age 13 years. Perilobular fibrosis and inactive micronodular cirrhosis. Note absence of fatty degeneration. Trichrome stain, $\times 200$. **C:** Gross appearance of the liver at autopsy at age 13 years with a uniform, finely granular cut surface.

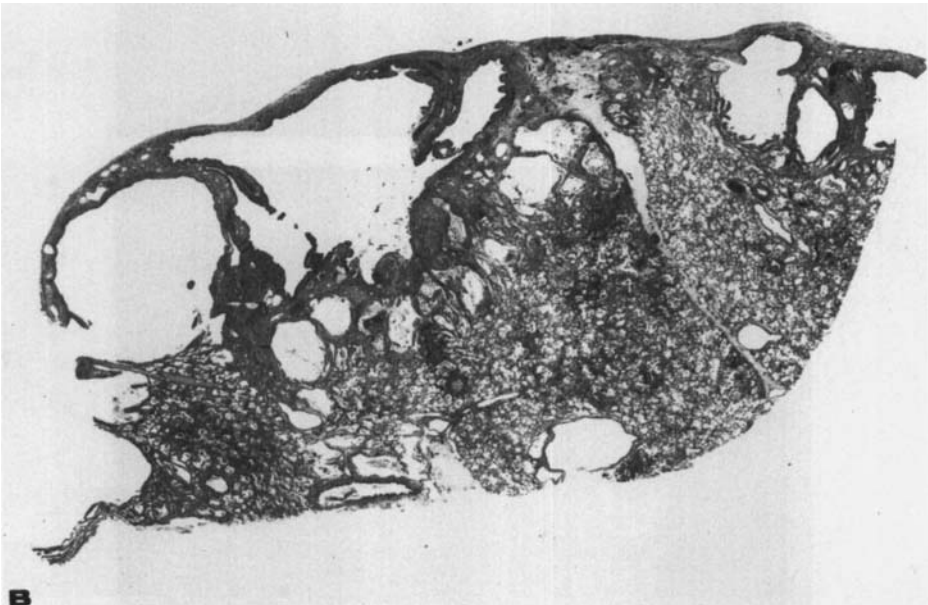
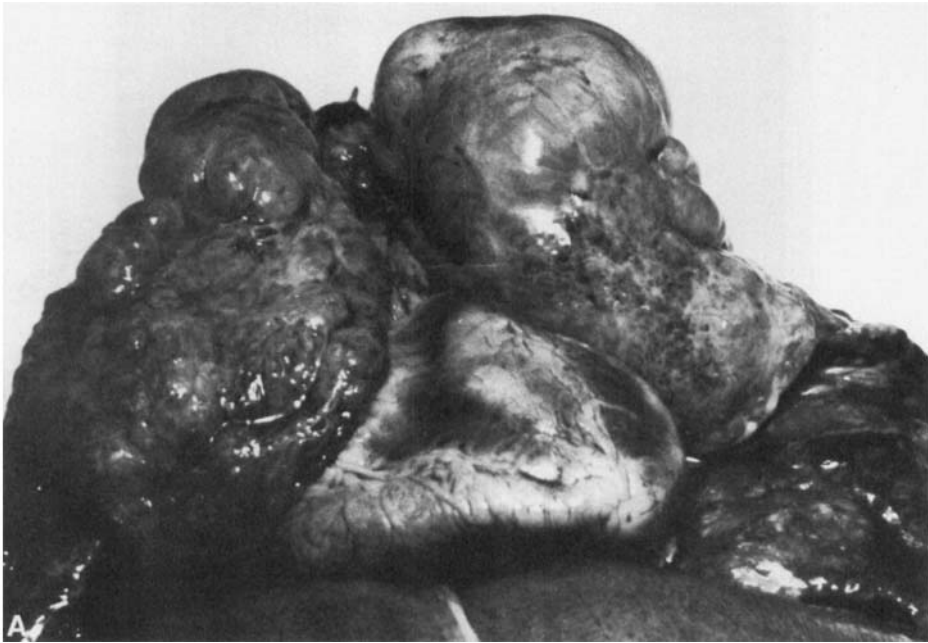


Fig. 9. Patient 3, pulmonary emphysema. **A:** Gross appearance of the lungs at autopsy: bilateral pulmonary emphysema with cyst formation. **B:** Whole mount of lung with emphysema and cysts of different sizes. Hematoxylin and eosin.

How does one interpret the combination of cerebral calcifications, cirrhosis, and emphysema in three brothers, with cerebral aneurysms in two of them? Review of the literature on FINCC shows other rare associations such as hydrotic ectodermal dysplasia [Copeland et al, 1977], phenylketonuria [Parker and Landing, 1977], steatorrhea and pseudoobstruction [Cockel et al, 1973], glaucoma [Kousseff, 1980], and cystic astrocytoma [Morimota et al, 1984]. These findings are probably merely coincidental; however, it is highly unlikely that cerebral calcifications, cirrhosis, and emphysema present in each of our three patients represent chance concurrence. Of interest in this context is a new syndrome in adults characterized by a peculiar phenotype, hyalinosis of small vessels, FINCC, and, in one patient, a cerebral aneurysm [Rambaud et al, 1986]. We did *not* observe small vessel hyalinosis in our patients. Bilateral ganglia calcifications have also been described in association with osteopetrosis and renal tubular acidosis, an autosomal recessive syndrome due to carbonic anhydrase II deficiency [Sly et al, 1985]. The syndrome described by us evidently is due either to an autosomal or to an X-linked recessive mutation. Furthermore, our observations seem to indicate that FINCC is a causally nonspecific disorder that can occur as a component of several different syndromes.

The relationship of cerebral aneurysms with cerebral calcifications, cirrhosis, and emphysema is intriguing. However, we lack an adequate biochemical basis to postulate a testable pathogenetic hypothesis. Thorough examinations at autopsy of *all* organs, not only of the CNS, of patients with FINCC, evaluation of living sibs and other relatives, and a detailed clinical history of future cases will further contribute to a better understanding of this entity.

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REFERENCES

- Aicardi J, Goutières F (1984): A progressive familial encephalopathy in infancy with calcifications of the basal ganglia and chronic cerebrospinal fluid lymphocytosis. *Ann Neurol* 15:49–54.
- Babbitt DP, Tang T, Dobbs J, Berk R (1969): Idiopathic familial cerebrovascular ferrococalciosis (Fahr's disease) and review of differential diagnosis of intracranial calcification in children. *Am J Roentgenol Rad Ther Nuclear Med* 105:352–358.
- Barwich D (1976): Symmetrische Stammhirnganglienverkalkungen (Morbus Fahr) und ihr familiäres Vorkommen. *Nervenarzt* 47:253–257.
- Bolander H, Hassler O, Liliequist B, West KA (1978): Cerebral aneurysm in an infant with fibromuscular hyperplasia of the renal arteries. Case report. *J Neurosurg* 49:756–759.
- Boller F, Boller M, Gilbert J (1977): Familial idiopathic cerebral calcifications. *J Neurol Neurosurg Psychiatr* 40:280–285.
- Cockel R, Hill EE, Rushton DI, Smith B, Hawkins CF (1973): Familial steatorrhea with calcification of the basal ganglia and mental retardation. *Quart J Med [New Series]* 42:771–783.
- Constantinidis J, Aubert M, Tissot R (1978): Contribution a l'étude des calcifications pallido-dentelées (à propos de sept observations anatomo-cliniques). *Arch Suisses Neurol Neurochir Psychiatr* 122:237–251.
- Copeland DD, Lamb WA, Klintworth GK (1977): Calcification of basal ganglia and cerebellar roof nuclei in a mentally defective patient with hydrotic ectodermal dysplasia. Analysis of intracranial concretions by electron microprobe. *Neurology* 27:1029–1033.
- Dinkel L (1971): Zur Klinik der zerebralen Kernkalzinose. *Münch Med Wochenschr* 113:1346–1353.

- Harati Y, Jackson JA, Benjamin E (1984): Adult onset idiopathic familial brain calcifications. *Arch Intern Med* 144:2425-2427.
- Hastings-James R (1970): Lenticulodentate calcification. *Radiology* 97:571-576.
- Kousseff BG (1980): Fahr disease. Report of a family and a review. *Acta Paediatr Belg* 33:57-61.
- Löwenthal A, Bruyn GW (1968): Calcification of the striopallidodentate system. In Vinken PJ, Bruyn GW (eds): "Handbook of Clinical Neurology." Amsterdam: North-Holland Publishing Company; New York: Elsevier Publishing Co., pp 703-725.
- Melchior JC, Benda CE, Yakovelev PI (1960): Familial idiopathic cerebral calcifications in childhood. *Am J Dis Child* 99:787-803.
- Morimoto K, Mogami H, Ozaki K (1984): Fahr's disease associated with cystic astrocytoma. *Eur Neurol* 23:265-268.
- Moskowitz MA, Winickoff RN, Heinz ER (1971): Familial calcification of the basal ganglions. A metabolic and genetic study. *N Engl J Med* 285:72-77.
- Parker CE, Landing BH (1977): Coincidence of Fahr disease and phenylketonuria. *J Pediatr* 91:273-275.
- Rambaud JC, Gallian A, Touchard G, Morel-Maroger L, Mikol J, Van Effenterre G, Leclerc JP, Le Charpentier Y, Haut J, Matuchansky C, Zittoun R (1986): Digestive tract and renal small vessel hyalinosis, idiopathic nonarteriosclerotic intracerebral calcifications, retinal ischemic syndrome, and phenotypic abnormalities. A new familial syndrome. *Gastroenterology* 90:930-938.
- Rodin AE, Chabali R, Minella PA, Wharton CH, Singla, P (1982): Cerebral berry aneurysm in a child. *J Pediatr* 100:156-159.
- Schéda W (1970): Beiträge zur Histopathologie der Fahrschen intrazerebralen Gefäßverkalkung. *Psychiatr Neurol Med Psychol* 22:413-418.
- Seth HN, Roy S (1972): Idiopathic non-arteriosclerotic cerebral calcification (Fahr's disease)—A case report. *Indian J Pathol Microbiol* 15:47-51.
- Sly WS, White MP, Sundaram V (1985): Carbonic anhydrase II deficiency in 12 families with the autosomal recessive syndrome of osteopetrosis with renal tubular acidosis and cerebral calcification. *N Engl J Med* 313:139-144.

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