Fibromuscular Dysplasia and the Brain

Observations on Angiographic, Clinical and Genetic Characteristics

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SUMMARY **The angiographic, clinical, and genetic characteristics of fibromuscular dysplasia (FMD) are reviewed in 37 patients (mean age 48 years) selected from a pool of 4000 angiograms of carotid or vertebral arteries. FMD was a neglected pathogenic factor in 28 patients with hemorrhagic or ischemic cerebral lesions. The aneurysms found in 19 patients had conventional appearance and were mainly located in the internal carotid or middle cerebral arteries and on the same side as the most affected cervical artery, which suggests that aneurysms and FMD are pathogenically related. A clinical syndrome is presented where headache, ECG-abnormalities, hypertension, mental distress, tinnitus, vertigo, arrhythmia, TIA, and syncope are frequent components. Hemicrania, sometimes combined with ipsilateral Horner's Syndrome, was found in patients with advanced lesions in the carotid artery of the same side. An associated occurrence of stroke in pedigrees, especially among young and middle aged females, indicates that FMD in the majority of cases is inherited as an autosomal dominant trait with reduced penetrance in males.**

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EARLIER reports of fibromuscular dysplasia (FMD), to be reviewed in part two, have essentially contributed the same picture of FMD: an angiopathy often associated with hypertension, most often discovered in middle aged females, characterized by dysplastic vessel wall deformations multifocally spread within branches of the aorta, and a high frequency of intracranial aneurysms. The association of FMD with aneurysmal arterial disease, recognized early[1] as well as with an abundance of congenital abnormalities and an increasing number of reports of familial occurrence, raises the suggestion that FMD is a congenital mesenchymal disorder.

In a recent ultrastructural study, Bragin and Chercaso 1979[2] suggest that FMD is based on a uniform morphogenetic process in which the leading role is played by fibroblast-like transformation of smooth muscle cells. Each one of the three major structures of the vessel wall (tunica intima, media, and adventitia) might be deformed by dysplastic lesions. Unfortunately, histological verification of aortocranial lesions is available only in a minority of cases. Thus, the clinical diagnosis in most cases has to be made with angiography. However, the characteristic macroscopic appearance and topography of the lesions are considered pathognomonic in the cervical as well as in the renal arteries.

In this study, 37 patients from Karolinska Hospital are reviewed with special regard to the angiographic, clinical, and genetic features. We have found it important to discuss our results in the light of 1100 cases of FMD, with various locations, reported in the literature (part two).

Patients and Methods

Thirty females and 7 males with FMD (mean age 48 years, range 24–70) were found by scrutinizing 4000 consecutive angiographies of carotid or vertebral arteries performed at Karolinska Hospital during 1970–78. The material and the reason for the angiography are presented in table 1 *A* and *B*. All case histories were studied in detail and 24 survivors could be traced and investigated. A thorough analysis was made of the angiographic findings at admission, and also of the previous medical history, the family occurrence of vascular diseases, the findings at ECG and clinical examination, and the blood groups. A pedigree was constructed for each patient with special regard to the vascular system. Whenever possible, the relatives were interviewed and their medical records examined. In total, 92 cephalic arteries were examined (table 2*A*). A complete 4-vessel examination was performed in 8 patients, and 3 of the cephalic arteries were examined in 13 patients. Five patients had bilateral and 11 unilateral carotid angiographies. In all patients, the specific cerebrovascular diagnoses "ischemic" or "hemorrhagic cerebral" lesion were based on clinical symptoms and signs, angiography and examination of cerebrospinal fluid, and in addition on computed tomography in one third of the cases. Electrocardiography was performed at least once in 30 patients, and the findings were classified according to the Scandinavian modification of the Minnesota Code.[3]

Results

Angiographic characteristics

FMD-lesions were noted in about two-thirds of the investigated vessels (table 2*A*). Nine out of 11 patients with vertebral lesions also had an involvement of one or both carotid arteries. Fourteen of the 25 patients in whom bilateral carotid angiography was performed had bilateral FMD.

The appearance of the lesions on angiograms was classified into three main groups according to Osborne and Anderson.[4] The first group (Type 1) presented with the classical "string of beads" pattern with multiple constrictions of the lumen in the affected vessel segment. Between the constrictions, the lumen is of

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TABLE 1 *Clinical Features in 37 Cases of Aortocranial Arterial FMD*

A.	General	
	Sex Males	7
	Females	30
	Age (years)	
	Mean	47.8
	Range	24–70
B	Diagnosis at admission	
	Cerebral hemorrhage	
	Hematoma (intracerebral)	3/37
	Subarachnoidal	18/37
	Cerebral ischemia	
	Infarction	3/37
	TIA	4/37
	Brain tumour	4/37
	Horner's Syndrome	3/37
	Epilepsia	1/37
	Tinnitus	1/37
C.	Previous symptoms	
	Headache	25/32
	Mental distress	14/29
	Tinnitus	11/29
	Vertigo	10/29
	Arrhythmia	9/29
	"TIA"	8/26
	Syncope	8/29
	Carotodyni	5/24
	Epilepsy	4/26
	Impaired hearing	3/24
	"Abdominal angina"	2/24
	Angina pectoris	1/24
	Flush-attacks	1/24
	Claudicatio	0/24
	Myocardial infarction	1/24

		Families n = 23	Members n = 166	Males	Females
D.	Family history				
	Hypertension	12/23	13	6	7
	Stroke	12/23	18	3	15
	Myocardial infarction	5/23	5	4	1
	Migraine	9/23	8	0	8
	Impaired hearing or deafness	8/23	11	8	3
E.	Clinical findings				
	ECG-abnormalities	17/30			
	Hypertension	18/37			
	Carotid bruit	5/25			
	Horner's Syndrome	4/37			
	Skeletal deformities	1/24			
	Dextroposition of the heart	1/24			
	Abdominal or iliac bruit	0/24			
F.	Blood groups				
	A	11/24			
	B	2/24			
	AB	0/24			
	O	11/24			
G.	Analysis of suggested pathogenetic alternatives				
	Diabetes	6/37			
	Immunological disorders	0/37			
	Ergotamin medication	9/24			
	Oral contraceptives	1/24			

TABLE 2 *Angiographic Findings in 37 Patients*

		a.car. dx.	a.car. sin.	a.vert. dx.	a.vert. sin.
A.	Investigated vessels				
	Number of investigated vessels (N = 92)	30	32	10	20
	FMD-changes (N = 60)	23	26	4	7

		Number of vessels (N = 60)	Number of patients (N = 37)
B.	Classification		
	Type 1	40	23
	2a	9	6
	2b	6	4
	2a and 2b	—	1
	3	5	3

		Females	Males	Total
C.	Intracranial aneurysms			
	a. carotis interna	9	2	11
	a. cerebri media	6	2	8
	a. cerebri anterior	3		3
	a. pericallosa	2		2
	a. basilaris	1		1

normal width or wider (fig. 1). Patients with a single constriction (focal stenosis) at the typical site were classified as belonging to this group in the present study, since "beaded" lesions were found in other arteries. The second group presented with either (Type 2a) tubular stenosis with or without further constrictions (fig. 2a), or (Type 2b) tubular stenosis with aneurysmal dilatations in the stenotic segment of the vessel (fig. 2b). The third group (Type 3) presented with semi-circumferential lesions ["atypical fibromuscular dysplasia"]. As a rule, the lesions are concentrated to one side of the vessel wall, which shows a diverticulum-like smooth or corrugated outpouching (fig. 3).

All lesions were of the same main group when several arteries were affected. Both kinds of the second group were found concomitantly in one patient.

In most of the patients, the lesions were found in the characteristic vessel segment adjacent to the second cervical vertebra. Only one patient had a probable extension of type 1 reaching into the intracranial portion of the internal carotid artery. Two patients had types 1 and 2a involving the proximal part of the vessel next to the bifurcation. One of these had a marked stenosis of both internal and external carotid arteries at the bifurcation on one side; the diagnosis was ascertained after surgery.

Twenty-five intracranial aneurysms were found in 19 patients with aneurysms. One of these also had a large arteriovenous malformation in the region of the sylvian fissure (fig. 4). The majority of the aneurysms were located in the internal carotid or middle cerebral

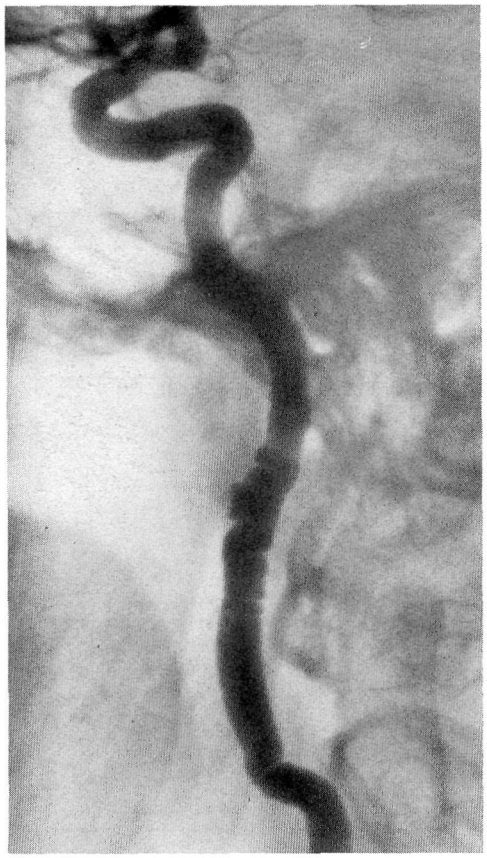

FIGURE 1. *The classical "string of beads" pattern with multiple constrictions of the lumen (type 1).*

arteries and on the same side as the most affected cervical artery. All aneurysms had the macroscopic appearance of the classical "berry-aneurysms."

Clinical characteristics

The diagnoses at admission (the reasons for angiography) are presented in table 1*B*. Seven patients with symptoms corresponding to the supply of the affected vessel were found to have ischemic lesions. No aneurysms were found at angiography in three cases with hematoma and two cases with subarachnoid bleeding. The majority of the 21 hemorrhagic cases, however, had aneurysmal bleedings. In one case with hematoma, the bleeding source was an arteriovenous malformation. Three patients admitted with Horner's syndrome had advanced FMD-changes (type 2b in 2 patients) in the internal carotid artery of the same side.

A majority of the patients had a history of multiple recurrent symptoms (table 1*C*). Headache was the most common symptom. It was reported in 25 of 32 patients (78%), 12 of these were of the vascular unilateral type and 13 were characterized by widespread throbbing or pressure. Six of the patients had migraine symptoms since childhood or adolescence, but, in the majority of the cases with headache, the onset was less than 10 years before admission. Five patients had carotodyni (recurrent or persistent pain of one side of the neck). Almost 50% of the patients gave a history of mental distress such as depression and anxiety. About one third had a history of pulsatile tinnitus, vertigo, arrhythmia (paroxysmal tachycardia), or TIA (focal neurological deficit of less duration than 24 h), whereas syncope and epilepsy were somewhat less frequent. The onset of these symptoms was generally less than five years before admission. There was generally a remarkable congruence between clinical symptoms and topography of FMD-lesions (table 3).

Abnormal ECG's were found in 17 of 30 investigated patients (table 4). In 24 of these patients, the investigation was performed at a stage when acute phase reactions or increased intracerebral pressure could be excluded. There was a high frequency of T-abnormalities without coexistent QRS- or ST-abnormalities.

Hypertension (Blood pressure 160/90 or higher in patients under 40, 175/105 or higher in the group 40 years of age or older, or a previous history of hypertension) was found in almost 50% of the cases. The duration was less than 10 years in 6 cases, more than 10 in 4 cases, and unknown in the rest of the cases. Only 9 out of 19 patients with aneurysms also had hypertension. In the whole hemorrhagic group, hypertension was found in two thirds of the cases.

Genetic characteristics

One third of the patients had a family history (table 1*D*) among first degree relatives (parents, siblings or children) of stroke, hypertension, migraine, or impaired hearing, whereas myocardial infarction and claudication were rare. Of special interest are families where two or several members — mainly females — had a stroke before middle age. Eight of these pedigrees are presented in figure 5.

Data available on 166 family members (first degree relatives) and, if stroke or hypertension were used as criteria for suspected FMD, 28 individuals seemed to be affected. Stroke among relatives of FMD-patients were several times more frequent among females than among males. The mean age at which stroke occurred is 53 years (table 1*D*).

The blood group distribution was analyzed in the search of further associated features, but did not show any significant difference when compared with the average of the Swedish population (table 1*F*).

Scrutinizing various other suggested pathogenetic possibilities (table 1*C*), we did not find any remarkable features.

Diagnosis, therapy, and prognosis

FMD had been a neglected diagnosis in most of our cases. It was only at a reinvestigation of the angiograms that this angiopathy was recognized. One of our patients, a 30 year old woman with TIA, exhibited advanced stenosis at the left carotid bifurcation and, because of atypical localization, the diagnosis could only be proven after surgery. A carotid bruit was not a regular finding in the present material. It was only to be found in cases with advanced stenosis.

The aneurysmal bleedings were operated by conven-

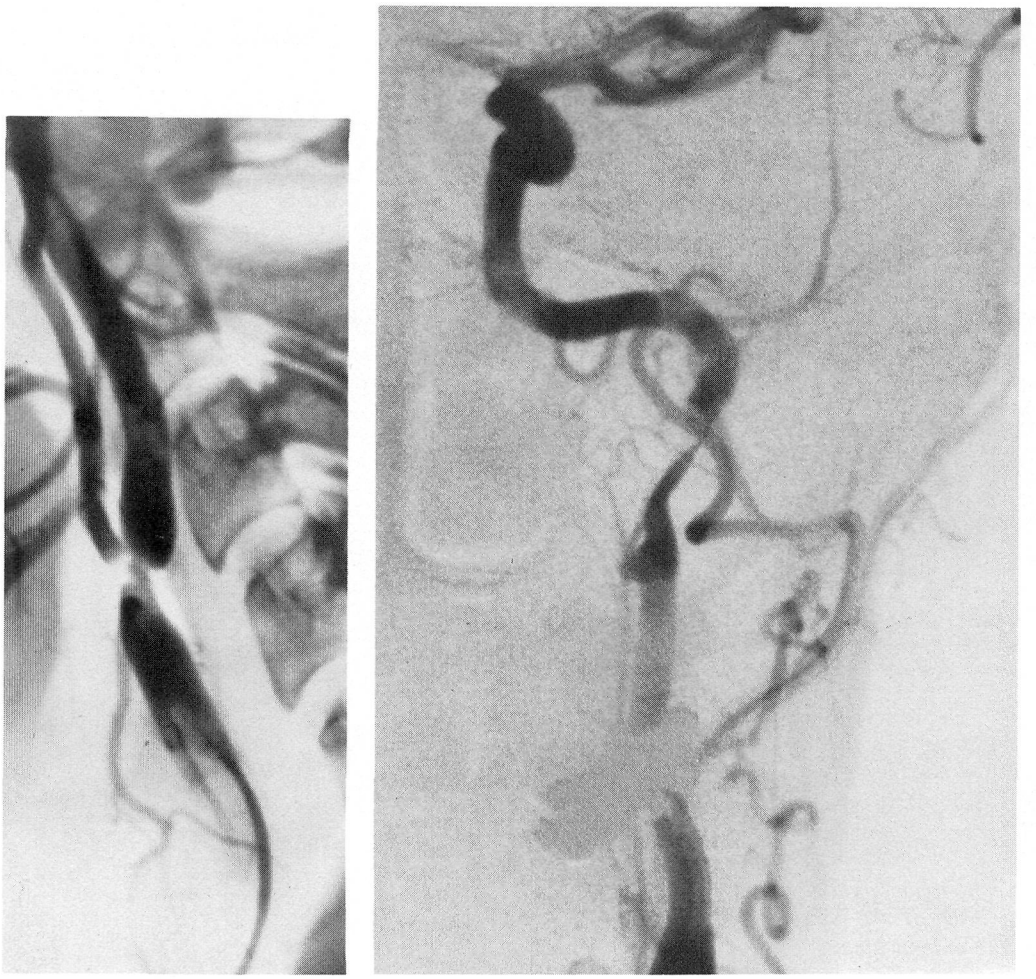

FIGURE 2. *a) Tubular stenosis with or without further constrictions (type 2a). b) Tubular stenosis with aneurysmal dilatations in the stenotic segment of the vessel (type 2b).*

tional techniques. Four of these patients died. Only one of our patients has had carotid surgery (endarterectomy) so far, whereas four patients received platelet inhibiting therapy against TIA. During an observation time of 6, 13, 18, and 24 months respectively, no further attacks have been reported.

After a mean observation time of 48 months, 24 out of 37 patients are known to survive.

Discussion

Angiographical characteristics

In the present series, 19 out of 37 patients (51%) had totally 25 intracranial aneurysms, which means that four patients had two or more aneurysms. In another study,[5] aneurysms were found in 27 of 72 patients (39%), but only 50% of the patients had had bilateral angiography.

Stehbens[6] believed that the intracranial aneurysms in patients with FMD are a secondary effect of hypertension. However, since only 9 out of our 19 patients with aneurysms also had hypertension, this could not be the only cause.

The aneurysms have no pathognomonic appearance, and are most common on the same side as the most affected extracranial carotid artery in our experience. This strongly suggests that the two disorders are pathogenically related. When aneurysms are combined with hypertension, the risk of cerebral hemorrhage is increased. Two-thirds of the hemorrhagic cases had hypertension compared to 50 percent in the total material.

Clinical characteristics

The mean age of our patients, 48 years, is in good agreement with other patients with aortocranial FMD (see part two).

More than 50% of our patients had hemorrhagic lesions which is slightly more than earlier reported. This difference might reflect a higher percentage of neurosurgical patients among our patients or more refined methods to separate bleedings from infarctions.[7]

Ischemic lesions were considered in 31% of our patients based on the present clinical state or the previous medical history. In most patients, only slight or moderate FMD changes could be found in the cervical arteries, whereas stenoses of hemodynamic significance and occlusions were rare. In some patients,

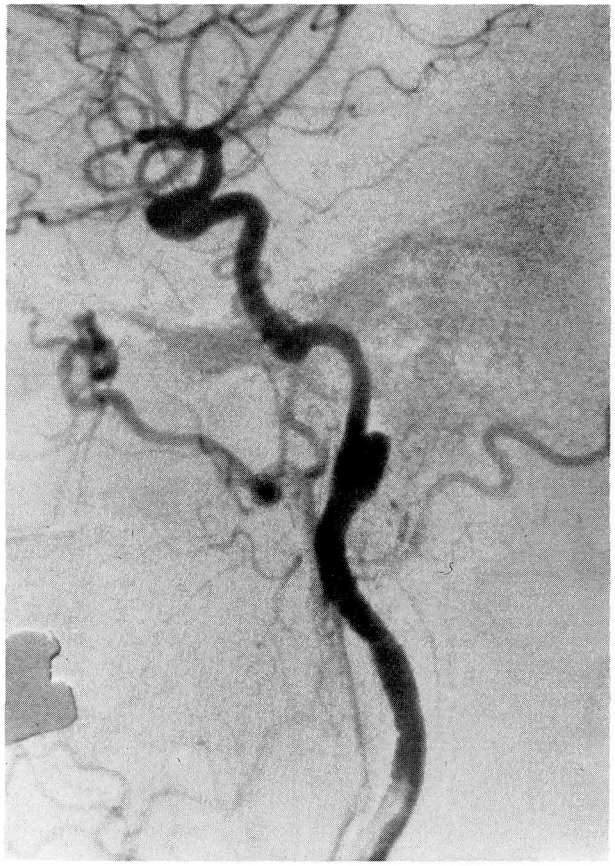

FIGURE 3. *Semi-circumferential lesion (type 3), concentrated to one side of the vessel wall which shows a diverticulum-like outpouching.*

TABLE 3 *Topographical Comparison of Symptoms and Lesions*

	N	Extension of FMD: car sin	Extension of FMD: dx	vert sin	vert dx
Headache unilat					
sin	7	6	1		
dx	5	1	4		
Carotodyni					
sin	2	2			
dx	1		1		
Vertigo	10	8	8	3*	1*
Tinnitus	11	7	7	4	3
TIA					
sin	1	1	1		
dx	3	3	1		
bilat	2	2	1	1	1
Syncope	8	7	5	1	1
Horner's Syndrome					
sin	3	3			
dx	1		1		

*Nine vertebral arteries were not examined in this group.

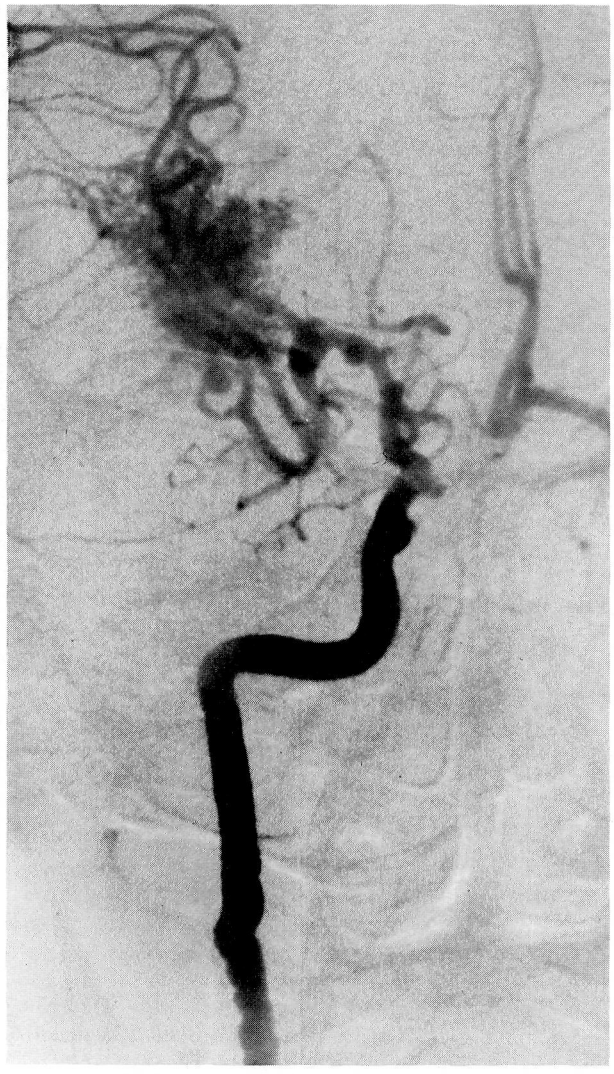

FIGURE 4. *Arteriovenous malformation in the region of the sylvian fissure.*

however, an additional hormonal (oral contraception in one of our patients and in a few reported ones) or mechanical factor (neck trauma in one patient, bending of the head in a few reported patients) could be noted. Coexistent atherosclerotic or ulcerated lesions[8] must also be considered.

We were able to interview and reinvestigate most of our survivors, all information that we received was related to angiographic findings (table 3). A high frequency of various recurrent symptoms was found. There was a striking association between symptoms and angiographically demonstrated lesions. A causal relationship between lesions and symptoms seems undisputable in the majority of cases. The symptoms were generally not related to uncontrolled hypertension and their intermittent nature makes intracranial aneurysms an unlikely cause.

Headache is the most common symptom in earlier studies, recognized in more than 90 percent of the patients with renal FMD.[9] A correlation between carotid artery disease and headache has earlier been

TABLE 4 *Electrocardiographic Findings* in 30 Patients with FMD*

Normal	13†	
Abnormal	17	
T-abnormality only		7
T-abnormality + ST-depression		5
ST-depression only		1
High R-amplitude		4
Q-wave suggestive of previous myocardial infarction (M-code)		1
Arrhythmia (occasional supraventricular ectopic beats)		1

*Codeable according to the Scandinavian modification of the Minnesota code.
†One of these patients developed negative ST and T 6 months after admission.

suggested and various mechanisms have been discussed.[10, 11] We would like to point out the possible role of vasoactive substances released from platelets[12, 13] activated by turbulence in narrowed arteries. Pulsatile tinnitus is common in patients with multiple arterial abnormalities, which was recently reviewed by Nevins, Lyon and Kim, 1978.[14] The Horner's syndrome was in our patients probably caused by pressure on the sympathetic fibres originating from the stellate ganglion in the posterior wall of the carotid sheath. Similar cases were reported by West et al.[15] All our subjects with syncope had carotid lesions, which possibly could affect the nerve fibres of the carotid sinus. Vertigo is probably related to stenosis of the vertebral arteries, but unfortunately only six of these patients had vertebral angiography.

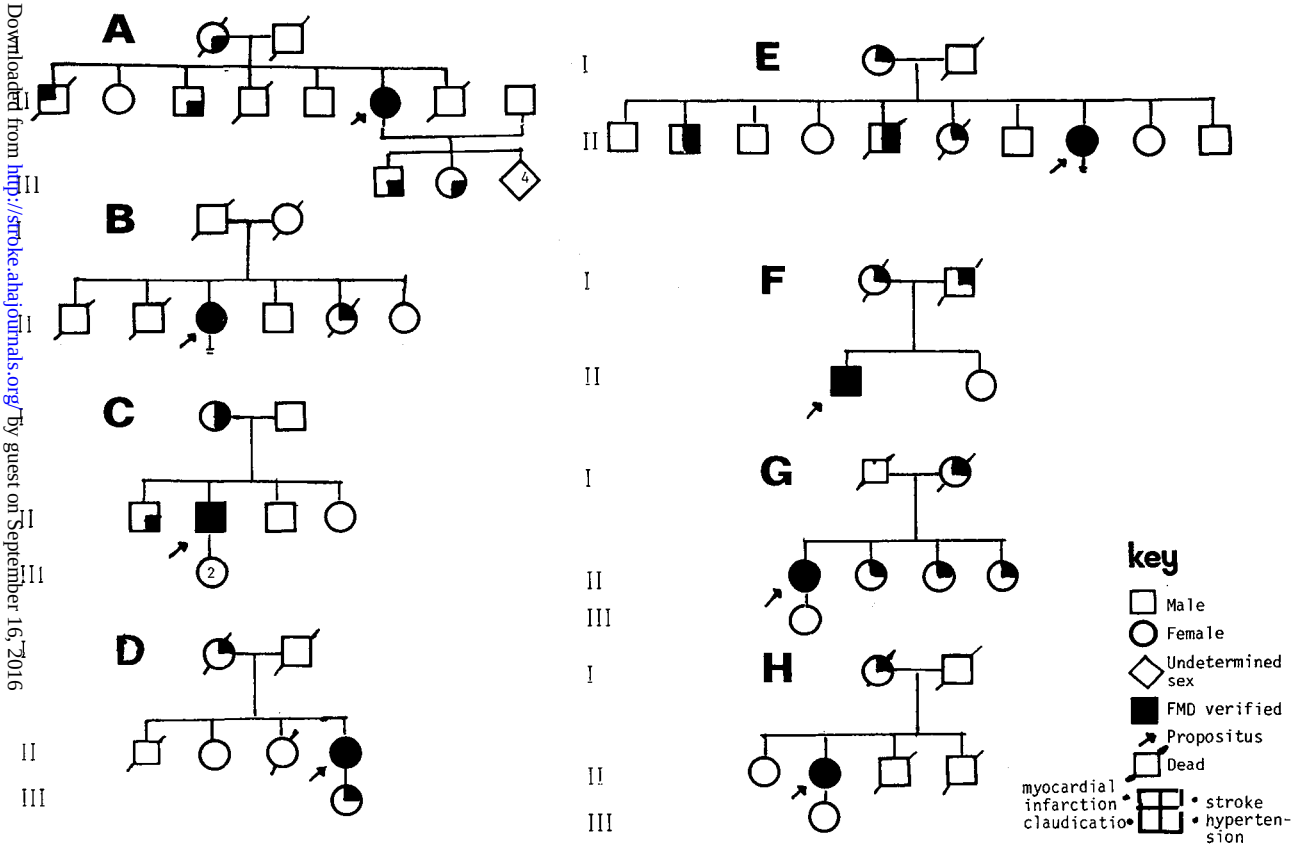

FIGURE 5. *A. Propositus: 51 year old female with hypertension, admitted twice with subarachnoid hemorrhage. Mother, sister (II-3) and two children, 30 and 20 years of age respectively (III-1, III-2) had hypertension. B. Propositus: 66 year old female with subarachnoid hemorrhage without hypertension. Sister (II-5) had subarachnoid hemorrhage (aneurysmal) at 47. C. Propositus: 33 year old male admitted with TIA and hypertension. Mother had hypertension since 46 and cerebral infarction at 59 and brother (II-1) had hypertension since 36. D. Propositus: 59 year old female with intracerebral hematoma without aneurysms. Mother had stroke at 72, daughter had subarachnoid hemorrhage without aneurysm at 26. E. Propositus: 38 year old female with subarachnoid hemorrhage. Mother had three strokes from the age of 55, three siblings (II-2, II-5, II-6) had strokes before the age of 50. F. Propositus: 40 year old male with subarachnoid hemorrhage (aneurysmal). Parents suffered strokes at 50 and 40 years of age respectively. G. Propositus: 59 year old female with myocardial infarction at 47, hypertension and progressive senile dementia since 52. Admitted with subarachnoid hemorrhage (aneurysmal). Mother had two strokes after 65 and three sisters (II-2, II-3, II-4) had strokes at 50–60 years of age. H. Propositus: 55 year old female with hypertension, admitted with subarachnoid hemorrhage (aneurysmal). Mother had stroke at 60, one brother (III-4) died at 24 with kidney malformation.*

Impaired hearing was not a frequent finding and a male preponderance in pedigrees (table 1*D*) makes FMD an unlikely cause.

Electrocardiographic abnormalities were not frequent in an earlier study of patients with renal FMD.[16] The electrocardiograms of patients in the present study, who had a higher mean age and therefore possibly more extensive vascular lesions, showed an unexpectedly high frequency of abnormalities without coexistent QRS- or ST-abnormalities. These might reflect unspecific myocardial damage, including small subendocardial infarctions. They could, however, be of vegetative origin in some patients caused by increased intracranial pressure, which, however, could be excluded in most of our patients. As FMD has been reported in the coronary arteries[17] including their branches supplying the sinus node and A-V node,[18] it is tempting to suggest that such changes might have contributed to the high frequency of ECG-abnormalities as well as of previous arrhythmia found in the present study.

Genetic characteristics

The pedigrees show a remarkable accumulation of stroke, hypertension and migraine occurring in about 35% of the families. Of special interest are families where two or several members had stroke or hypertension in their adolescence or middle life. Pedigrees, recently presented,[19, 20] suggest in these patients a dominant trait with reduced penetrance. Patients without a family history of such disorders may represent new mutations or have relatives with clinically "silent" disorders.

The inherited character of FMD is further supported by our observation[19] that stroke among family members (first degree relatives) was several times more frequent among females than among males and that the mean age was only 53 years.

This is in contrast to a population study of stroke of different etiologies in Stockholm 1973–1978 (Mettinger and Söderström to be published) where in about 2000 cases of stroke before the age of 55, a clear male preponderance (1.6:1) was noted.

In our experience and in the literature, heart infarction and claudication are rare manifestations of FMD. Furthermore, heart infarctions before the age of 50 are, in pedigrees, (table 1*D* and ref. 20) more common among males and are probably not reliable criteria to suspect FMD as there is a contamination of atherosclerosis.

The results indicate that FMD is a hereditary vascular disease with a wide spectrum of cerebrovascular accidents among young and middle aged patients, mainly females. Morphological studies at autopsies or biopsies would most probably confirm a diagnosis of FMD.

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