Fibromuscular Dysplasia and the Brain

II. Current Concept of the Disease

Karl Lennart Mettinger, M.D.

SUMMARY Eleven hundred cases from the literature of fibromuscular dysplasia (FMD) are reviewed including 300 cases with aortocranial lesions. The male-female ratio is 1:2, and the prevalence seems increased among Caucasians. The clinical diagnosis of FMD is made by angiography, ten years earlier in patients with hypertension (mean age 39 years) than in those with cerebrovascular symptoms (mean age 50 years). Segmental dysplastic lesions are found mainly in primary aortic branches. All age groups may be affected and follow-up studies give evidence for stationary as well as slowly progressive lesions. A multifactorial hypothesis of etiology is presented: congenital minor lesions of tunica media might predispose to aneurysms and to an abnormal fibroproliferative response to mechanical or circulatory stimuli. The association of FMD and intracranial aneurysmal disease in females is discussed. Inheritance as a dominant trait with reduced penetrance in males is suspected. Current aspects on morphology, symptomatology and clinical management are presented.

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Fibromuscular Dysplasia (FMD) is an angiopathy with increasing clinical recognition. It has a well established place in the pathogenesis of renovascular hypertension since renal artery stenoses have been recognized in about one third of the patients. Although the first patient was described by Leadbetter and Burkland 1938, it is mainly during the last decade that multiple arterial involvement outside the renal arteries has been reported including about 300 cases with aortocranial arterial lesions.

Occurrence and Natural Course

About 1100 patients with FMD have been reported in the literature, (tables 1-3), and about 300 of these show aortocranial arterial involvement. Most patients are Caucasian (only 30 Negroid cases). One third are male and about two thirds are female (table 3). In a study of 819 consecutive routine autopsies, only 9 patients with FMD were found, suggesting an incidence of about 1 percent.

The mean age of reported aortocranial FMD is about 50 years, range 0-90 (table 3). Renovascular lesions seem to be diagnosed earlier, the mean age of 320 patients being 39 years. A Japanese report, mainly including young males, might represent an entirely different entity of disease. As FMD has been found in children, it may be a slowly progressive disease affecting the cerebral functions only at a later stage. Follow-up studies, with repeated angiographies in 106 patients observed during less than 9 years, give evidence for both progressive and stationary lesions, whereas regression has not been reported.

Etiology

Several hypotheses have been suggested. Many observations suggest a congenital component of the disease which will be further discussed. Stretching of arteries at movements of the head or abnormally mobile kidneys could possibly cause repeated microtraumata, but this has also been suggested as a pathogenic factor in atherosclerosis affecting the more proximal vessel segments. Experimental studies give contradicting results as to whether or not mural ischemia, caused by thrombotic or mechanical obliteration of vasa vasorum, plays a role in the evolution of dysplastic lesions. Ischemia and irritation could possibly cause mutation of a cell, which suggests a monoclonal nature of dysplastic lesions as of atherosclerosis. It has also been suggested, but not substantiated, that hormonal, metabolic and immunological factors or even ergotamine medication might produce FMD.

Evidence of a Congenital Origin

It should be emphasized that the vessel wall of the fetus is developed from mesenchymal islands. Embryologically, the tunica muscularis develops first on the main trunk of an artery and, later, independently, on its side branches. The proximal portion of the internal carotid artery is derived from the third aortic arch, the rest of the artery from the left dorsal aorta. This could explain the topographical characteristics of FMD which is rarely found in the proximal portion.

Associated findings of renal artery or renal abnormalities in 15 per cent of the patients with renovascular FMD, give further support to a congenital origin of FMD (table 2). The true prevalence of such abnormalities in patients might be even higher as they are not always searched for or reported.

Familial occurrence of FMD has been reported in a few cases; recently an abundance of anomalies of the urinary tract, hypertension or suspected otosclerosis were found in families of some Swedish patients with FMD. As for familial occurrence of hypertension, conflicting results have been reported in patients with renal FMD. Only recently, pedigrees of FMD-patients have been presented suggesting that FMD is inherited as a dominant trait with reduced penetrance in males. It has been suggested that case histories of vascular dis-
orders, before the age of 50, might be useful criteria for suspecting FMD in pediatrics. This inevitably includes a major group of middle aged men with heart infarction caused by atherosclerosis. The conclusion of such a study is that FMD has the same prevalence in males as in females, which is strongly contradicted by accumulated data (table 3). Thus any attempt to calculate risks, as was made by the same investigators, should be postponed until pedigrees can be based on verified diagnoses.

The etiology of FMD has remained an enigma. A multifactorial hypothesis, including a congenital component, seems reasonable. As FMD has been demonstrated to be progressive in some cases, it is likely that the disease might start as minor lesions of congenital origin which might predispose to an abnormal fibroproliferative response to mechanical or circulatory stimuli.

Morphological Features

About 50 cases with histologically verified FMD of the cervical arteries have been studied. The various types of lesions have been found to be identical with the changes in the renal arteries. A recent ultrastructural study suggests that all forms of FMD are based on a uniform morphologic process where the leading role is played by fibroblast-like transformation of smooth muscle cells.

The present histopathological classification, suggested by Harrison and McCormack and recently revised by Stanley et al., is based on the location of the major lesions within the vessel wall. The angiographic and macroscopic classification (52,74,75,113 and part one) include a spectrum of lesions corresponding to a mixture of histological patterns: the beaded type of lesion is generally caused by medial fibroplasia (60–85%) with alternating ridges (fibroproliferative tissue or collagen disrupting the smooth muscle) and microaneurysms (deficient smooth muscle or lamina elastica interna) in the media layer. Tubular stenoses (elongated narrowing of the lumen) and focal ringshaped or eccentric stenoses are less frequent and can be associated with any histological type of FMD. Macroscopic aneurysms, outpouchings, and dissections are thought to represent complications of FMD and should not be classified in a distinct histopathological group.

Intracranial Aneurysms

A correlation between FMD and intracranial aneurysmal disease, first assumed by Palubinska and Newton, is well established today. In 284 reported patients with aortocranial FMD (table 3) there were 61 patients with intracranial aneurysms (21%) and 20 of these had two or several aneurysms. The true frequency of aneurysms might be by more than 50 percent — as indicated in studies with a more com-

<table>
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<th>Artery</th>
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<td>and vertebral*</td>
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<tr>
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*Overlapping of materials.

Table 2

<table>
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<tr>
<th>Association</th>
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<td>Intracranial aneurysms</td>
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<tr>
<td>Arteriovenous malformation or fistula</td>
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<td>Aberrant renal arteries</td>
<td>53, 75</td>
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<td>Renal ptosis</td>
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<tr>
<td>Renal hypo-, dys-, aplasia</td>
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<tr>
<td>Bladder pelvis</td>
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<td>3</td>
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<tr>
<td>Osteosclerosis or conduction defects</td>
<td>92</td>
<td>2</td>
</tr>
<tr>
<td>Dysplastic retinal degeneration</td>
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<td>1</td>
</tr>
<tr>
<td>Hallux valgus</td>
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<td>1</td>
</tr>
<tr>
<td>Pes cavus</td>
<td>61</td>
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<td>Pectus excavatum</td>
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<td>Endocardial fibroelastosis</td>
<td>9</td>
<td>1</td>
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<tr>
<td>Anatomical variation of His bundle</td>
<td>90</td>
<td>2</td>
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<tr>
<td>Pheochromocytoma</td>
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<td>Absent fifth lumbar vertebra</td>
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<td>Moyamoya</td>
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<tr>
<td>Dextroposition of the heart</td>
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The location of aneurysms and absence of hypertension in many patients with FMD suggests that the aneurysms are manifestations of the morphologic process of FMD itself rather than secondary effects of hypertension as presumed earlier. Recently published autopsy cases give histopathological evidence of intracranial aneurysmal diseases with distinct characteristics with regard to sex, topography, and multiplicity. It seems reasonable to postulate that one of these disorders is closely related to, or in many cases even identical with, FMD.

The symptoms corresponding to widespread FMD lesions in the arterial tree. However, asymptomatic cases exist.

**Clinical Manifestations**

It is characteristic that FMD might cause hemorrhagic as well as ischemic cerebral lesions, including TIA, sometimes in the same individual. A well investigated patient group showed a higher frequency of bleedings (21/37) and hypertension (18/37) than earlier patient groups (23 and 16 — 30 percent respectively; Table 3 and ref. 37, 48). Pathophysiological aspects were discussed in part one. Earlier investigators give contradicting reports of neurological symptoms besides cerebrovascular accidents. Sandok and coworkers advocated caution in relating symptoms, even strokes, to FMD, as such an evident association might be false because of the selection of the patients from a neurological centre. Manelfe et al, reviewing their own and others experiences, emphasized the polymorphism of clinical symptoms. None of them believed that any clinical syndrome could be related to FMD. However, both reports were based on hospital records and no systematic search of symptoms and signs was done.

It should be noted that neurological symptoms are not infrequent in patients with renovascular FMD. Foster et al reported headache in 50 out of 56 patients and an 18-year old girl had a transient stroke. Hunt et. al concluded, from his experience of 133 cases, that symptoms were rare and that only two patients had TIA or stroke, which was a lower frequency than in the atherosclerotic group. However, patients with more than one morbid event (myocardial infarction or stroke) were excluded. In none of these studies, a thorough neurological investigation was motivated or reported. However, absence of neurological symptoms in such patients would not be conclusive, as the mean age in patients with aortocranial FMD is almost a decade higher and FMD is reported to be progressive.

In patients with a thorough investigation, it was possible to recognize a clinical syndrome where headache, ECG-abnormalities, hypertension, mental distress, tinnitus, vertigo, arrhythmia, TIA, and syncope are frequent components. The symptoms correspond to widespread FMD lesions in the arterial tree. However, asymptomatic cases exist.

**Diagnosis and Therapy**

Evidence of proliferation of aneurysmal disease, as well as of FMD, give contradictory reports of neurological symptoms besides cerebrovascular accidents. Sandok and coworkers advocated caution in relating symptoms, even strokes, to FMD, as such an evident association might be false because of the selection of the patients from a neurological centre. Manelfe et al, reviewing their own and others experiences, emphasized the polymorphism of clinical symptoms. None of them believed that any clinical syndrome could be related to FMD. However, both reports were based on hospital records and no systematic search of symptoms and signs was done.

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The cause of this phenomenon is still obscure. The results of carotid surgery using various techniques\(^7\), \(^8\), \(^9\), \(^10\), \(^11\), \(^12\) in 50 reported patients seem promising, even if the observation time most often has been short. Our own limited experience of antiplatelet drugs indicates that medical therapy is relevant especially in cases not accessible for surgery, and it will be further evaluated.

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References


87. Stavenow L, Henriques B, Ekberg M, Bergentz SE, Hood B: Combination of fibromuscular hyperplasia, renal aplasia, hypoplasia or dysplasia and othosclerosis occurring in the same individual or the same family. Acta Med Scand 203: 357-362, 1978


89. Ekelund L, Gerloch J, Molin J, Smith C: Roentgenological aspects of fibromuscular dysplasia. Diagnostica 19: 433-446


95. Fierez M: Letter. Ergotism-fibromuscular hyperplasia rela-


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