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.

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 1,8,55,93). 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 vasaorum, 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-

From the Departments of Neurology and Neuroradiology, Karolinska Institute, Stockholm, Sweden.
All correspondence should be directed to: Dr. K.L. Mettinger, Department of Neurology, Karolinska Hospital, S-104 01 Stockholm, Sweden.
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 comprehensive approach.

**Table 1  Review of Various FMD-localizations**

<table>
<thead>
<tr>
<th>Artery</th>
<th>First report</th>
<th>References</th>
<th>Total number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal</td>
<td>1938</td>
<td>1,2,3,5,6,72,73</td>
<td>695</td>
</tr>
<tr>
<td>Celiac</td>
<td>1964</td>
<td>48,72,74,75,76</td>
<td>10</td>
</tr>
<tr>
<td>Mesenteric</td>
<td>1964</td>
<td>9,20,48,74-77</td>
<td>14</td>
</tr>
<tr>
<td>Splenic</td>
<td>1964</td>
<td>77</td>
<td>1</td>
</tr>
<tr>
<td>Iliac</td>
<td>1964</td>
<td>8,34,72,75,77-84</td>
<td>30</td>
</tr>
<tr>
<td>Aorta</td>
<td>1965</td>
<td>34,85</td>
<td>2</td>
</tr>
<tr>
<td>Humeral</td>
<td>1965</td>
<td>34</td>
<td>1</td>
</tr>
<tr>
<td>Cystic</td>
<td>1965</td>
<td>34</td>
<td>2</td>
</tr>
<tr>
<td>Gastric</td>
<td>1965</td>
<td>34</td>
<td>1</td>
</tr>
<tr>
<td>Femoral</td>
<td>1965</td>
<td>34</td>
<td>1</td>
</tr>
<tr>
<td>Occipital</td>
<td>1965</td>
<td>34</td>
<td>1</td>
</tr>
<tr>
<td>Coronary</td>
<td>1965</td>
<td>34</td>
<td>2</td>
</tr>
<tr>
<td>Internal carotid and vertebral*</td>
<td>1965, 1968</td>
<td>7-70,74,119,122,123</td>
<td>383</td>
</tr>
<tr>
<td>External carotid</td>
<td>1965</td>
<td>10,34,58</td>
<td>24</td>
</tr>
<tr>
<td>Middle cerebral</td>
<td>1965</td>
<td>8,21,34,39,48,54</td>
<td>7</td>
</tr>
<tr>
<td>Anterior cerebral</td>
<td>1965</td>
<td>8,34,48</td>
<td>5</td>
</tr>
<tr>
<td>Ant. communicating</td>
<td>1965</td>
<td>34</td>
<td>1</td>
</tr>
<tr>
<td>Basilar</td>
<td>1965</td>
<td>34,67</td>
<td>2</td>
</tr>
<tr>
<td>Axillary</td>
<td>1967</td>
<td>86,87</td>
<td>2</td>
</tr>
<tr>
<td>Hepatic</td>
<td>1967</td>
<td>9,74,88,89</td>
<td>5</td>
</tr>
<tr>
<td>Subclavia</td>
<td>1969</td>
<td>15,48</td>
<td>2</td>
</tr>
<tr>
<td>Internal mammary</td>
<td>1974</td>
<td>48</td>
<td>3</td>
</tr>
<tr>
<td>Posterior cerebral</td>
<td>1974</td>
<td>26</td>
<td>1</td>
</tr>
<tr>
<td>Sinus node</td>
<td>1976</td>
<td>90</td>
<td>2</td>
</tr>
</tbody>
</table>

*Overlapping of materials.

orders, before the age of 50, might be useful criteria for suspecting FMD in pedigrees. 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.

**Table 2  Review of Associated Findings**

<table>
<thead>
<tr>
<th>Aneurysms</th>
<th>References</th>
<th>Total number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial aneurysms</td>
<td>7-70,74</td>
<td>72</td>
</tr>
<tr>
<td>Arteriovenous malformation or fistula</td>
<td>29,43,74,94</td>
<td>5</td>
</tr>
<tr>
<td>Aberrant renal arteries</td>
<td>53,75</td>
<td>37</td>
</tr>
<tr>
<td>Renal ptosis</td>
<td>75,94</td>
<td>60</td>
</tr>
<tr>
<td>Renal hypo-, dys-, aplasia</td>
<td>91,92</td>
<td>5</td>
</tr>
<tr>
<td>Bifid renal pelvis</td>
<td>92</td>
<td>3</td>
</tr>
<tr>
<td>Osteosclerosis or conduction defects</td>
<td>92</td>
<td>2</td>
</tr>
<tr>
<td>Dysplastic retinal degeneration</td>
<td>64</td>
<td>1</td>
</tr>
<tr>
<td>Hallux valgus</td>
<td>64</td>
<td>1</td>
</tr>
<tr>
<td>Pes cavus</td>
<td>61</td>
<td>1</td>
</tr>
<tr>
<td>Pectus excavatum</td>
<td>61,92</td>
<td>2</td>
</tr>
<tr>
<td>Endocardial fibroelastosis</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Anatomical variation of His bundle</td>
<td>90</td>
<td>2</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>1,92</td>
<td>3</td>
</tr>
<tr>
<td>Neurofibromatosis</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Absent fifth lumbar vertebra</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>Moyamoya</td>
<td>56</td>
<td>1</td>
</tr>
<tr>
<td>Dextroposition of the heart</td>
<td>119</td>
<td>1</td>
</tr>
</tbody>
</table>
I would like to call the attention to some pertinent observations in the cooperative study of aneurysms and subarachnoid hemorrhage based on 2,672 cases of aneurysms. This study clearly showed that intracranial aneurysmal diseases with distinct characteristics with regard to sex, topography, and multiplicity are unlikely to occur together with more aneurysms. Furthermore, in all age groups location at the internal carotid artery is about twice as common in females, and there is a similar female preponderance for aneurysms of the middle cerebral artery. Multiple aneurysms are likely to be restricted to these two arteries. On the other hand, aneurysms of the anterior cerebral arteries are most common among men and are unlikely to occur together with more aneurysms. These findings, never explained in a satisfactory way, suggest the possible existence of at least two separate 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 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 disease complicated by aneurysms.

**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 center. 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 aortic 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-anomalies, 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. It has been shown that both types of lesions may start as minor defects in the vessel wall which could be overlooked at angiography and autopsy. The characteristic appearance and the location of lesions are pathognomonic. As FMD is recognized earlier in the renal arteries, we suggest that renal angiography should be performed routinely (beside cervical angiography) in young and middle aged stroke patients with hypertension. In patients — especially middle aged females — with multiple vague symptoms such as headache, tinnitus, vertigo, arrhythmia and syncope the diagnosis of FMD may be considered. Unfortunately the diagnosis can only be verified after angiography or operation.

FMD lesions (especially stenoses) with atypical location may have identical appearance with atherosclerosis. Less problematic differential diagnoses are arteritis, arterial spasm and carotid hypoplasia. In "stationary waves", first described by Wickbom, Bartley and Theander the "string of beads" pattern is more regular and seen in the entire vessel. Typically, there is no dilatation between narrowings.
The cause of this phenomenon is still obscure.

The results of carotid surgery using various techniques\(^1\), \(^2\), \(^3\), \(^4\), \(^5\) 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.

Acknowledgments

I would like to thank professor Eric Kugelberg and professor Torgny Greitz who have inspired the present study. In the preparation of the manuscript I have also had valuable advice from Professor Ulf Lindblom, Professor Jan Lindsten, and Associate Professors Lars Edström and Lennart Kaijser. The study was supported by grants from the Swedish Society for Medical Research and the Karolinska Institute.

References

99. Fievez M: Letter. Ergotism-fibromuscular hyperplasia rela-
Fibromuscular dysplasia and the brain. II. Current concept of the disease.
K L Mettinger

Stroke. 1982;13:53-58
doi: 10.1161/01.STR.13.1.53
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1982 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/13/1/53

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/