Intracranial Fibromuscular Dysplasia: Report of Two Cases, One With Autopsy Verification

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SUMMARY

We report two patients with fibromuscular dysplasia (FMD) involving intracranial arteries. In the first patient the diagnosis was made at autopsy. Both patients were symptomatic from FMD, and in addition, displayed unusual hormonal abnormalities which may well have contributed to the genesis or evolution of FMD.

FIBROMUSCULAR DYSPLASIA (FMD) is a rare, segmental, nonatheromatous arterial disease of unknown etiology involving small to medium-sized arteries, predominantly affecting women. It was first described in 1938 by Leadbetter and Burkland. FMD most commonly affects the renal arteries; involvement of the superior mesenteric, celiac, hepatic, external iliac, and axillary arteries have been reported. Involvement of the cephalic arteries was first documented angiographically by Palubinskas and Ripley in 1964, and confirmed histologically by Connett and Lausche in 1965. Subsequent reports described cases of FMD of the cervical internal carotid arteries, vertebral arteries alone, or associated with internal carotid arteries, the occipital artery, and the external carotid artery. Our contribution to the literature consists of two cases, the first of which was verified at autopsy.

Case Reports

Case 1 (S.G.)

A 22-year-old right-handed woman (college student) was admitted to the hospital on November 29, 1972, complaining of headaches and difficulty with speech. In the past the patient had complained of nonspecific headaches and menstrual irregularities. She had been treated for the latter with birth control pills for approximately six years: Ovulin in 1966, Norinyl from 1967 to 1971, and Ortho-Novum 1/50 in 1972. Ten days prior to admission, she complained of left-sided headaches, a sore throat and pain in the left ear. She was treated by her family physician with antibiotics and eardrops for "tonsillitis." The next day she noted increasing headaches and experienced intermittent difficulty with her speech. Three days prior to hospital admission, she was admitted to the school infirmary complaining of severe left temporal headaches, numbness over the right side of her face, transient diplopia, occasional difficulty in using her right hand, difficulty in expressing herself, and increasing lethargy.

On examination, the blood pressure was 130/70 mm Hg, the pulse was 90 beats, and the temperature was 97°. Pertinent findings included a fairly alert, cooperative young woman with an expressive, dysnomic aphasia and a right central facial weakness. The neck was supple, and the tonsils were slightly enlarged. Harsh bruits were heard over both orbits, louder on the left side. Carotid bruits and cardiac murmurs were absent.

Neurological examination demonstrated a right hemiparesis with slight weakness of the right upper extremity and an extensor plantar response on the right side. Sensory modalities were intact. No signs of extrapyramidal or cerebellar dysfunction were noted.

The only pertinent laboratory findings included a diffusely abnormal EEG, taken on November 30, 1972, with widespread excess of 2 to 3 cycles per second activity, as well as diffuse increase of theta activity in a 5 to 6 cycles per second range. The EEG findings were suggestive of diffuse cortical dysfunction.

On November 30, the patient was started on dexamethasone (Decadron), 10 mg i.v., and placed on a maintenance dose of 4 mg i.m. every six hours. On December 1, a dynamic Tc-pertechnetate brain scan was done. Earlier it revealed decreased isotopic activity over the left hemisphere, followed by increased perfusion over the affected hemisphere. No flow abnormality could be detected in the cervical portions of the cephcal arteries. The static scan was essentially normal.

A left carotid angiogram revealed rattle deformity of the proximal portion of the internal carotid artery, which appeared to be occluded. No abnormalities of the external carotid were noted. The supraclinoid segment of the internal carotid was filled via the ophthalmic artery and showed slight irregularities of its lumen. Filling of the intracranial branches of the internal carotid artery was delayed but complete, indicating marked slowing of the intracranial circulation. The posterior communicating and posterior cerebral arteries were also visualized, the latter showing laminar flow (fig. 1).

A right retrograde brachial arteriogram revealed a hypo-plastic internal carotid artery with no irregularities of its cervical portion. The intrapetrous and intracavernous segments were abnormally and irregularly narrow. The supraclinoid portion of the internal carotid artery was normal. The branches of the middle cerebral and of the anterior cerebral arteries were also normal except for minimal bowing of the pericallosal vessels to the right, indicating edema of the left hemisphere. The right vertebral artery was normal. However, the basilar artery ended rather abruptly at the level of the superior cerebellar arteries (fig. 2).

On the basis of the arteriographic findings, we suspected an arteritic process or perhaps dissecting aneurysms of the intracavernous portions of the internal carotid arteries. FMD was not suspected. A few hours after the arteriograms had been completed, the patient became progressively
more stuporous. On December 3, 1972, she had a right hemiplegia and was totally aphasic. Shortly thereafter, she exhibited decerebrate posturing, especially of the right limbs. An emergency tracheostomy was performed. In spite of restricted fluid intake and dexamethasone, on December 4, the patient's pupils became dilated and fixed, and within a short period of time, respirations ceased. The patient was artificially ventilated for three days. Each day an EEG indicated electrocerebral silence. The patient was declared neurologically dead on December 7, 1972.

At autopsy, except for focal, severe bronchopneumonia the pertinent gross findings were limited to the head and neck. The brain weighed 1,580 gm and was soft and mushy, with moderate gyral swelling. The vessels of the circle of Willis were thin, patent, and without atherosclerotic changes. The intracavernous portion of the left internal carotid artery was quite enlarged and distended, and on cut sections it was occluded by a pale, red thrombus. The opposite intracavernous internal carotid artery showed marked reduction of the lumen. The extracranial segment of the carotid arteries was normal.

Microscopically, both internal carotids showed severe subintimal fibrous hyperplasia resulting in uniform tubular constriction of the lumen. The fibroblasts appeared mature and showed deposition of a moderate amount of collagen among which numerous smooth muscle cells were noted on Masson staining. The internal elastic membrane showed severe reduplication, ranging from short multilayered spindles to full circumferential accessory elastic laminae. The media was of normal thickness and showed focal loss of muscle fibers with collagenization within the inner coat. The external elastica showed a mild and variable degree of disruption and hypoplasia. A thrombus with early organization occluded the lumen of the intracavernous segment of the left carotid artery (fig. 3). A smaller organizing mural thrombus was incorporated along the fibrotic lining of the right intracavernous internal carotid. The basilar artery showed a similar subintimal fibroplastic and elastic change with scant mural thrombus. The vertebral, anterior, middle, and posterior cerebral arteries were not affected. The retinal artery showed a subintimal cushion of fibroelastic tissue. No vessel showed histiocytic infiltration, chronic inflammation, or atheromatous deposit. The left internal carotid was normal in the lower neck, but underwent mild fibroblastic subintimal hyperplasia above the level of arteriographic injection. Brain sections showed extensive recent necrosis of the temporal cortex, basal ganglia, and brainstem associated with marked autolytic changes.

**Figure 1.** (Case 1) Left carotid arteriogram. The rattail deformity of the proximal portion of the internal carotid artery is clearly visualized (arrow). It can be followed up to the anterior arch of CI. Note the filling of the supracranial portion of the internal carotid artery via the ophthalmic artery and filling of the branches of the middle cerebral artery.
No other vascular abnormalities were noted in any abdominal or thoracic organs. Branches of the coronary, hepatic, and splenic arterial systems were normal. The renal arteries were not available for study.

The extensive and varied vascular changes seen in some of the intracranial arteries of this patient, and to a lesser extent in the cervical portions of the left internal carotid artery, can best be classified as intimal fibroplastic variants of arterial fibromuscular dysplasia. The marked increase in subintimal muscle fibers and total lack of foam cells, atheromatous deposits, or inflammatory reactions seem sufficient to rule out an atherosclerotic process. Antiovulant angiopathy, in which papillary endothelial hyperplasia or focal nodular thickening, at times accompanied by a three-layered organized thrombus, is a characteristic change noted, and bears little resemblance to the lesions noted in our patient.

Case 2 (G.W.)

A 55-year-old right-handed housewife was admitted to the hospital on March 20, 1973, because of chronic vaginal bleeding. She complained of mild generalized headaches. Later she had several seizures, starting with clonic movements of the right side of the face and upper extremity, with adverse eye movements to the right. The third of these seizures became generalized. In the postictal state, she exhibited mild right-sided weakness and appeared confused. Examination revealed a slightly lethargic and confused woman, disoriented to place and time, and clearly unable to name objects. Loud bruits were heard over both carotid and subclavian arteries in the neck. A soft bruit was audible in the right temporal region. A grade 2 systolic bruit was heard along the right midtemporal region. No pupillary or funduscopic changes were present. Muscle strength was normal, and no abnormal reflexes were noted.

An EEG (performed on March 29, 1973) revealed slow background activity, with a high amplitude, arrhythmic, delta focus in the right posterior head region. Periodic, lateralized epileptiform discharges (PLEDs) were seen in the right parieto-occipital region. A $^{99m}$Tc-pertechnetate brain scan performed on April 2, 1973, was normal. On April 6th, left carotid and right retrobrachial arteriograms were performed showing bilateral changes typical of FMD, involving the cervical segments of the internal carotid and vertebral arteries (figs. 4 and 5).

In the intracranial branches of the left internal carotid artery, there were sausage-like deformities of at least two branches of the middle cerebral artery and of the callosal marginal artery; there were focal narrowing followed by segmental dilatation in portions of these vessels. Repeat
arteriography one week later showed identical changes, thus excluding the possibility of arterial spasm. Biopsy of the right superficial temporal artery revealed moderate thickening of the intima by dense connective tissue. The internal elastic membrane was intact, and the muscularis and adventitial layers were normal. (While intimal fibrosis is a change seen in FMD, in itself it was not considered positively diagnostic in this patient since these changes could also be attributed to aging.) Although focal dilatation interposed between constricted segments of intracranial arteries can be seen in other pathological entities such as amphetamine arteritis, meningitis or vasculitis, we do not feel that these diagnoses were applicable to our patient. She was placed on maintenance doses of phenobarbital and Dilantin; subsequently she had a transabdominal hysterectomy and was discharged neurologically normal.

Comments

FMD involving the intracranial portions of the internal carotid artery or its major branches has been described by several authors, based on arteriographical abnormalities. Hartman et al. and Pollock et al. have reported the only two cases of FMD involving the intracranial portion of the carotid artery. The diagnosis was made on the basis of detailed histological examination of both the intracranial and extracranial segments of the cephalic vessels. There are great similarities between our first patient and the patient described by Hartman et al., who was a 29-year-old woman with generalized fibromuscular hyperplasia who had had a stroke. The patient, who had been taking oral contraceptive medications for two years, died “when multiple arterial thromboses interrupted collateral circulation to the brain.” The clinical picture had been that of a progressive stroke, just as in our case. The brain scan had been negative. Arteriography had demonstrated occlusion of both cervical internal carotid arteries, as evidenced by reflux of dye into both intracranial internal carotid arteries “to a point just below the bifurcations.” Bilateral filling of the anterior and middle cerebral arteries was demonstrated to have occurred via the right vertebral artery on a right retrograde brachial arteriogram. As in our patient, following arteriography, Hartman’s case showed rapid deterioration of the neurological picture, with death occurring the following day. At autopsy, changes of intimal and medial fibromuscular hyperplasia (FMD) with disorganization of the elastic laminae were found in the internal carotid, coronary, renal, splenic, internal iliac, and femoral arteries. The lumina of the cervical segments of each internal carotid artery were either narrowed or occluded by intimal hyperplasia. The authors stated that “although the arterial dysplasia extended into intracranial segments, the distal lumina were patent and contained only postmortem blood clots from reflux filling.” No other evidence of intracranial FMD was found. According to the authors, “death ensued when collateral circulation provided by the right vertebral artery was interrupted by thrombus.” The authors suggested that the thromboses in the collateral circulation to the brain had caused the subacute and acute neurological disease in this young woman, inferring that these thromboses were related to the oral contraceptives. They did not feel justified in attributing a specific cause-and-effect relationship between oral contraceptives and the development of FMD and were careful to state that FMD does indeed also occur in men and in women who have not been on antiovulants. They surmised, nevertheless, that the FMD substrate “may be hormonally influenced” and that in their patient the antiovulant may have contributed to the florid progression of the generalized FMD.
The second case of histologically verified intracranial FMD was reported by Pollock and Jackson, in a 52-year-old man who died 35 days after admission for investigation of a progressive left hemiparesis. Angiography had disclosed "tubular stenotic lesions of the internal and external carotid arteries" very similar to those found in our first patient and also described by other authors, with occlusion of the carotid siphon between the ophthalmic and posterior communicating arteries. Biopsy of the right superficial temporal artery had shown changes typical of FMD. At autopsy, the walls of the right internal and left external carotid arteries were diffusely and symmetrically thickened, with marked luminal narrowing, commencing about 1 cm from their origin from the common carotid artery. The involvement affected the internal carotid artery throughout its cervical and intracranial course and terminated abruptly at the bifurcation. Similar changes also were present in the external carotid, lingual and facial branches. The internal carotid lumen was occluded between the ophthalmic and posterior communicating arteries. Histological changes of FMD were described. A remarkable feature was the ease with which the thickened intima detached from the media, with a cleavage plane between the internal elastic lamina and the media. The authors stressed the known increased risk of spontaneous dissection in this type of FMD.

It is not within the scope of our communication to describe the various histopathological types of FMD. They have been recently reported in detail by Stanley et al. These authors emphasized that detailed arteriographical investigation accounted for the initial identification of dysplastic lesions in all of their patients. Morphological and histological types of stenoses were often predictable from the arteriographical changes. However, since interpretations were not always correct, the authors stressed that arteriography alone is not sufficient to make the diagnosis of arterial fibrous dysplasia. A specific diagnosis can be made only by histological examination of the affected artery, if surgically accessible. Since FMD may involve vessels of wide distribution, biopsy of the superficial temporal artery has been used to help in the diagnosis of this pathological process (Anderson, Pollock, and ourselves). However, we suggest that the diagnosis is valid only when changes of FMD are histologically verified in the superficial temporal artery biopsy of very young patients. In older patients, changes due to aging may mimic those seen in FMD.

Apart from hormonal influences, it has been suggested that FMD occurs more frequently in arteries subjected to unusual mechanical forces (cervical arteries, renal arteries, etc.). Another factor contributing to the evolution of dysplastic lesions may be mural ischemia.
The long-term CT scan by showing the size, location and number of lesions had a good correlation with aphasia outcome. Those patients with large dominant hemisphere involvements, either one large or many smaller lesions, fared poorly while those with lesser lesions did better. Bilateral lesions, at times evasive clinically, helped to account for significant aphasia residuals.

APHASIA, or failure of communicative skills in symbolic language, has traditionally been studied by careful clinical observations, followed by pathological correlations. Indeed, the main historical proponents of aphasia localization, Broca and Wernicke, pioneered this approach in the second half of the nineteenth century. 1-3 Recently, investigators have been interested in the in vivo anatomical correlation of aphasias using neuroradiological tools. Benson and Patten 4 have used radioisotopic images in localizing aphasias. They have disparged the role of cerebral angiography, but others have sought to study aphasia with this modality. 5 Most recently, Mohr et al. 6 have made use of computerized axial tomography (CT) to more clearly define aphasia syndromes.

Compilation of serial aphasia evaluations, acute angiograms and radioisotintigrams, and the late follow-up CT scans was done. The aphasia evaluation and the neuroradiological information then were correlated in an attempt to find in vivo prognostic parameters.

References


SUMMARY Fourteen aphasic patients with acute onset of thromboembolic cerebrovascular insults demonstrable by angiography or radioisotintigrams who were available for long-term follow-up have been studied. Their aphasia evolution was compared with acute angiographical and radioisotintopic findings, and the lesions shown by follow-up computerized axial tomography (CT).

Angiographical site of occlusion, evidence of early reopening of occluded vessels, and radioisotintopic flow asymmetries including the "hot-stroke" luxury perfusion failed to correlate with aphasia outcome. Radioisotintopic static images were more helpful by depicting lesion location and number but lacked the definition seen on the CT scan.

The long-term CT scan by showing the size, location and number of lesions had a good correlation with aphasia outcome. Those patients with large dominant hemisphere involvements, either one large or many smaller lesions, fared poorly while those with lesser lesions did better. Bilateral lesions, at times evasive clinically, helped to account for significant aphasia residuals.
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