

Neuroanatomical Studies

Progressive cerebral vasculopathy and recurrent strokes due to intracranial fibromuscular dysplasia



Nicole B. Sur, MD^{a,*}, Sakir H. Gultekin, MD^b, Amer M. Malik, MD^a, Sebastian Koch, MD^a

^a University of Miami, Department of Neurology, 1120 NW 14th St, 13th Floor, Miami, FL 33136, United States of America

^b University of Miami, Department of Pathology, Holtz Children's Hospital, 1611 NW 12th Ave, R#2044, Miami, FL 33136, United States of America

ARTICLE INFO

Keywords:

Fibromuscular dysplasia
Ischemic stroke
Cerebrovascular disease
Rare causes of stroke
Cerebral vasculopathy

1. Introduction

Fibromuscular dysplasia (FMD) is a non-atheromatous, non-inflammatory vasculopathy of unknown etiology, affecting primarily small and medium sized arteries [1]. FMD is typically seen in women and the renal, extracranial carotid and vertebral arteries are most commonly affected. Very rarely, FMD has been reported in the intracranial carotid arteries and it is here that we report on a case of recurrent ischemic stroke in a middle-aged woman with autopsy-proven intracranial FMD.

2. Case report

A 55-year-old, right-handed, Romanian woman presented to clinic with complaints of word finding difficulty and right hemiparesis in 2005 for a second opinion. At age 44-years-old (yo) she developed her first symptoms of dysphasia and right sided weakness with a recurrence of similar transient symptoms at age 53 yo and again with worsening and persistent symptoms at age 55 yo. Brain MRI and MRA showed a remote left middle cerebral artery (MCA) infarct and left MCA narrowing just distal to the bifurcation (Fig. 1A).

She was on daily aspirin 81 mg and clopidogrel 75 mg. She had a history of untreated hyperthyroidism, mild hypertension, and mild dyslipidemia. She had no family history of stroke, vascular disorders, autoimmune disorders or connective tissue disorders. She did not smoke, consumed alcohol on rare occasion, and did not use illicit substances.

Physical exam was notable for mild conversational word finding

difficulty and mild right hemiparesis.

Lab workup revealed normal complete blood count, chemistry, lipid panel and glycosylated hemoglobin (A1C). Thyroid stimulating hormone (TSH) was low and free T4 level was normal. C reactive protein (CRP) was elevated at 7(?units?) and erythrocyte sedimentation rate (ESR) and antinuclear antibody (ANA) were normal. EKG revealed normal sinus rhythm. Brain MRA at our facility showed MCA stenosis along the distal M1 and proximal M2 branches. Subsequent digital subtraction angiogram (DSA) showed mild bilateral segmental beading of the mid-distal internal carotid arteries (ICA) and notable narrowing of the proximal left M2 branches (Fig. 1B).

A presumptive diagnosis of intracranial FMD was made. The patient was maintained on aspirin and clopidogrel for stroke prevention, and aggressive treatment of hypertension and dyslipidemia was continued.

Over the ensuing years she presented with recurrent infarcts in the left MCA territory. During these evaluations progression of the left MCA vasculopathy was noted (Fig. 1C) and a subclinical lesion became apparent in the right cerebral hemisphere. She then began to develop additional multiple right hemispheric infarcts. A repeat DSA at age 60 yo revealed the interim development of a right-sided vasculopathy involving a frontal M3 branch which subsequently began to involve the right proximal MCA.

At age 64 yo, she presented with complex partial seizures as well as a new acute ischemic stroke in the right anterior cerebral artery (ACA) territory with associated right A2 occlusion (Fig. 1D). She endured a complicated hospital course, which included Staphylococcal sepsis from an infected intravenous peripheral catheter. After her death, autopsy was restricted to her brain.

* Corresponding author.

E-mail address: nbsur@med.miami.edu (N.B. Sur).

<https://doi.org/10.1016/j.inat.2018.09.007>

Received 29 August 2018; Accepted 23 September 2018

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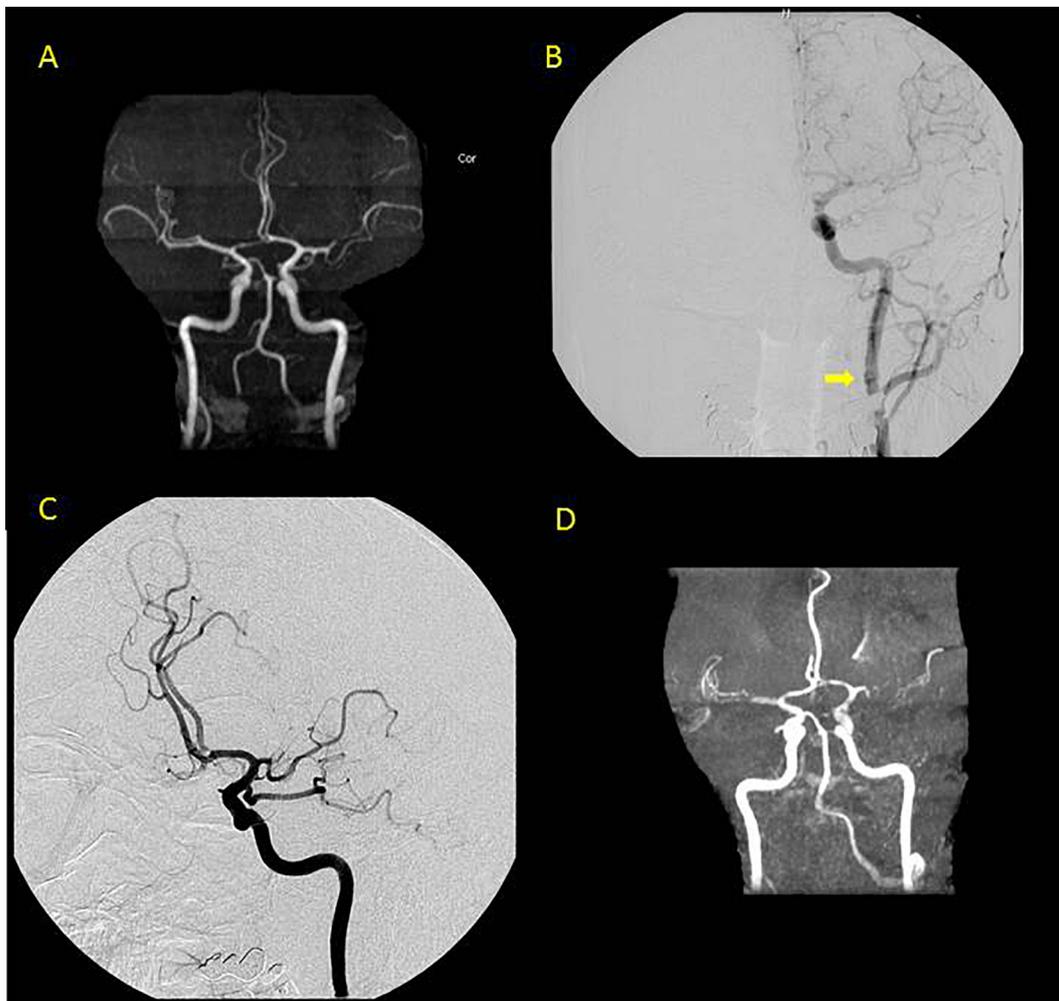


Fig. 1. MRA at age 55 yo showing left MCA M2 branch disease (A). DSA confirming the intracranial findings and showing mild cervical fibromuscular dysplasia (B; arrow). At age 60 yo, DSA shows left MCA occlusion (C). At age 63 yo, MRA shows progressive involvement of the proximal right MCA branches, the right A2 and right vertebral artery (D).

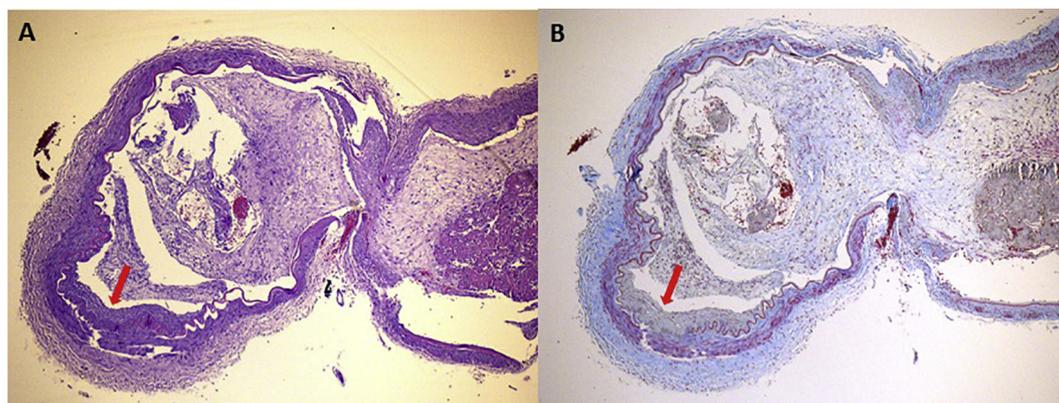


Fig. 2. Hematoxylin eosin (A) and trichrome (B) stains of the left MCA branches show eccentric intimal hyperplasia and disruption of internal elastic membrane (arrow). Collagen deposition was mild and the arterial media was preserved.

During the course of her illness she was extensively evaluated for other infectious and inflammatory causes of her vasculopathy. Lab workup revealed normal CBC and blood chemistries. TSH was low, but subsequently normalized with treatment of her hyperthyroidism. Thyroglobulin antibody and thyroperoxidase antibodies were normal. Repeat CRP was 1.5 mg/dL and ESR were normal. Lupus anticoagulant was positive on one occasion, though repeat testing on several

occasions was negative. Anticardiolipin antibodies, anti-beta 2 glycoprotein antibodies, Protein C and S, Antithrombin III and Factor V Leiden were negative. RPR, ANCA antibodies, ANA and serum protein electrophoresis were normal. Urine ceramide trihexoside was elevated, but Fabry's disease genetic testing was negative. She also had MR-based arterial wall imaging which showed no intracranial arterial wall enhancement. Cerebrospinal studies revealed normal cell count, glucose,

protein and immunoglobulin index. Oligoclonal bands were not detected and bacterial, viral and fungal cultures were negative. Herpes simplex virus Type 1 and 2 PCR, varicella zoster virus PCR, and syphilis serology in the CSF were negative. Doppler of her renal arteries was normal.

Gross pathological examination of her brain confirmed bilateral hemispheric remote cerebral infarcts and the acute right frontal infarction. There was concentric thickening of the larger proximal arteries of the Circle of Willis with intraluminal narrowing and occlusions of the right ACA and left MCA and its proximal branches.

Arterial sections from those arteries that were clinically symptomatic and radiologically involved in the Circle of Willis were analyzed. Eccentric intimal hyperplasia was seen in the bilateral MCAs intracranial terminal left ICA and anterior inferior cerebellar arteries, with only mild amount of collagen deposition (Fig. 2). Disruption of the internal elastic membrane was seen in the left MCA (Fig. 2). The basilar and bilateral posterior cerebral arteries were unaffected. Only the right ACA showed a mural mononuclear cell infiltrate, which we attributed to the acute terminal meningoencephalitis.

3. Discussion

The diagnostic evaluation of patients with stroke and intracranial vasculopathy remains a difficult task. We were able to exclude atherosclerotic, infectious, and inflammatory vasculopathies by serological investigations and by histopathology. Despite our patient having multiple vascular risk factors, all vessels examined showed no atherosclerosis. There was no evidence of inflammatory cell infiltration to suggest a vasculitis, either immune or infectious, except for the right ACA which showed acute inflammatory cell infiltration which we attributed to her terminal sepsis. Our patient also had hyperthyroidism but we believe that in the absence of overt clinical symptoms and autoimmune antibodies, a Graves disease-induced intracranial vasculopathy is unlikely. We cannot exclude moyamoya disease, however the sparing of the terminal ICA by angiography makes this less likely. The presence of extracranial FMD findings in the cervical ICAs on DSA, though mild, was suggestive of FMD as the cause of the intracranial vasculopathy, prior to autopsy confirmation.

FMD is classified by the layer of arterial wall most affected – the intima, media or adventitia. Medial FMD is the most common form and is characterized angiographically by the classic “string of beads” appearance [2]. Previous literature on FMD and intracranial FMD state that the intracranial form is typically characterized by intimal involvement, which was present in our case as well [2]. There are only rare reports of histologically-proven FMD of cerebral vessels and our case is unique in several ways. We were able to follow our patient for many years, and record the progressive nature of the vasculopathy. She had recurrent infarcts as the only manifestation of cerebral FMD. Previously reported cases of pathologically proven intracranial FMD have been complicated by other vascular pathologies that provide a clue to the diagnosis. These include the extension of pronounced cervical FMD intracranially [3], the presence of cerebral aneurysms [1,4], intracranial dissections [1], or intracranial arteries showing the typical beaded vessel appearance [3,5]. In many instances, death ensued shortly after clinical presentation due to severe infarction or

subarachnoid hemorrhage, hence leading to pathological examination. Pathological studies have largely shown intimal hyperplasia, with mature fibroblasts and moderate amount of collagen deposition, as well as disruption and duplication of the internal elastica, leading to vessel narrowing and occlusion [1,3]. These changes were also noted in our patient.

4. Conclusion

In summary we report a case of recurrent cerebral infarctions from a progressive cerebral vasculopathy due to intracranial FMD. The presence of mild cervical FMD led to a presumptive clinical diagnosis which was confirmed by histological examination.

Author contributions

Nicole B. Sur, drafting and revising the manuscript for intellectual content, final approval of the version published.

Amer M. Malik, revising the manuscript for intellectual content, final approval of the version published.

Sakir H. Gultekin, revising the manuscript for intellectual content, final approval of the version published.

Sebastian Koch, revising the manuscript for intellectual content, final approval of the version published.

Co-investigators

None.

Acknowledgements

None.

Author disclosures

Nicole B. Sur - reports no disclosures.

Amer M. Malik - reports no disclosures.

Sakir H. Gultekin - reports no disclosures.

Sebastian Koch - reports no disclosures.

References

- [1] S. Lummus, R. Breeze, M.S. Lucia, B.K. Kleinschmidt-DeMasters, Histopathologic features of intracranial vascular involvement in fibromuscular dysplasia, ehlers-danlos type iv, and neurofibromatosis i, *J. Neuropathol. Exp. Neurol.* 73 (2014) 916–932.
- [2] E. Touze, C. Oppenheim, D. Trystram, G. Nokam, M. Pasquini, S. Alamowitch, et al., Fibromuscular dysplasia of cervical and intracranial arteries, *Int. J. Stroke: Official Journal of the International Stroke Society* 5 (2010) 296–305.
- [3] I. Rinaldi, W.O. Harris Jr., J.E. Kopp, J. Legier, Intracranial fibromuscular dysplasia: report of two cases, one with autopsy verification, *Stroke* 7 (1976) 511–516.
- [4] M. Nakamura, S.K. Rosahl, P. Vorkapic, C. Forster, M. Samii, De novo formation of an aneurysm in a case of unusual intracranial fibromuscular dysplasia, *Clin. Neurol. Neurosurg.* 102 (2000) 259–264.
- [5] P. Pilz, H.J. Hartjes, Fibromuscular dysplasia and multiple dissecting aneurysms of intracranial arteries. A further cause of moyamoya syndrome, *Stroke* 7 (1976) 393–398.