Fibromuscular dysplasia: a differential diagnosis of vasculitis

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ABSTRACT

Fibromuscular dysplasia (FMD) involves small- and medium-sized arteries, being a well-known cause of hypertension in young Caucasian women, when renal arteries are involved. The etiology of FMD remains unknown, despite many theories. A genetic component is suspected to exist, because the pathology affects primarily Caucasians. Association between FMD and the HLA-DRw6 histocompatibility antigen has also been described. The major sites affected are renal, cerebral, carotid, visceral, iliac, subclavian, brachial and popliteal arteries. Clinical manifestations correlate with the affected site, arterial hypertension being a frequent symptom, resulting from the involvement of the renal arteries in 60%–75% of the cases. The diagnosis of FMD is made by histopathology and/or angiography. FMD can manifest as a systemic vascular disease, mimicking vasculitis. This understanding is important because vasculitis and FMD can both have a severe clinical course, but require distinct treatments. The differential diagnosis can be difficult in face of an atypical clinical presentation or lack of histopathologic confirmation. Isolated cases of FMD have been reported mimicking the following conditions: polyarteritis nodosa, Ehlers-Danlos's syndrome, Alport's syndrome, pheochromocytoma, Marfan's syndrome, and Takayasu's arteritis. Rheumatologists should be aware of this differential diagnosis. Treatment of FMD is recommended only in symptomatic cases, and consists in revascularization, which may be either surgical or via percutaneous transluminal angioplasty. In FMD, the effects of corticotherapy can directly and rapidly harm the vascular wall, aggravating the lesions.

Keywords: fibromuscular dysplasia, vasculitis, differential diagnosis.

DEFINITION, ETIOLOGY AND EPIDEMIOLOGY

Fibromuscular dysplasia (FMD) is a non-inflammatory, non-atherosclerotic vascular disease that involves small- and medium-sized arteries.[1–4] It affects predominantly Caucasian, thin women, aged between 15 and 50 years,[5] with no familial history of the disease.[1] The etiology of FMD remains unknown regardless of countless theories. A genetic component is believed to exist, because the disease affects mainly Caucasians and is associated with the HLA-DRw6 histocompatibility antigen. It is worth noting that FMD was first described in pairs of cousins and monozygous twins. The female predominance and frequent discovery during pregnancy suggest that estrogen plays a role in the pathogenesis of FMD.[6]

In addition to the findings suggesting genetic and hormonal etiologies, FMD has been reported in association with coagulation disorders, such as mutation of factor V Leiden, presence of antiphospholipid antibodies, mechanical stress,[5] and smoking.[3]

CLASSIFICATION

FMD is classified according to the arterial wall layer primarily affected as follows: intima, media, or adventitia. Dysplasia of the media is subdivided into medial, perimedial, and hyperplastic medial FMD.[7] Injury of the intima occurs in less than 10% of the patients, has a faster progression, and the histology shows circumferential deposition of collagen, with involvement of

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neither the lipid nor the inflammatory component. Arterial occlusion and simultaneous involvement of several medium-sized arteries, such as renal, carotid, and mesenteric, can occur mimicking necrotizing vasculitis.[7] Injury of the media is the most common (90% of the cases),[8] and has a slower progression. Injury of the adventitia is far less frequent.[3,5]

MAJOR ARTERIES AFFECTED

The frequency of FMD in the general population is lower than 1%, and reflects only the symptomatic form.[3] When involving the renal arteries, however, FMD is a well-known cause of hypertension in young Caucasian women.[1,2]

The renal arteries are affected in 60%–75% of the FMD cases. The lesion is limited to the distal two-thirds of the artery,[1,5] involving its branches in approximately 39% of the patients. The right renal artery is the dominant site of FMD, but the disease is bilateral in 39%–66% of the cases. The role of mechanical stress as the etiological factor is corroborated by the predominance of lesions in the right side, because the mobility of the right kidney is greater than that of the left kidney.[6]

Other vascular beds, however, can also be involved in 28% of the patients with FMD. Dysplastic lesions of the cephalic arteries are described in 25%–30% of the cases.[9] They occur in young adult women (85% of the cases), and the internal carotid artery is the most frequently affected site (95% of cases of involvement of the cephalic arteries), usually bilaterally (60%–85%); involvement of the vertebral arteries might coexist.[10] In addition, involvement of the following arteries has been reported: visceral; iliac; subclavian; brachial; and popliteal.[1,2,4,11,12]

CLINICAL FINDINGS

The clinical manifestations of FMD are determined by the artery affected and the degree of impairment of arterial blood flow. Cerebrovascular symptoms, resulting from FMD of the carotid artery, and arterial hypertension secondary to FMD of the renal artery are the most common manifestations. The involvement of other arteries can remain asymptomatic.[2,10,11]

In patients with FMD of renal artery, because of arterial obstruction, ischemia and progressive loss of the renal parenchyma occur, in addition to the clinical findings of arterial hypertension.[13]

The neurological manifestations comprise transient ischemic attacks, cerebral vascular accident, subarachnoid hemorrhage, and unspecific findings, such as headache, vertigo, tinnitus, hemianopsia,[9] ataxic paraparesis,[14] and mental alterations, depending on the brain area affected. The following have been reported in association with involvement of the nucleus caudatus,[8] due to arterial occlusion:[11] hyperorexia; excessive sleep; visual hallucinations; and missing days of work or school.

In the presence of stenosis of the coronary arteries, the patient might not have symptoms such as angina, but usually has electrocardiographic alterations, such as ventricular fibrillation, presence of Q wave, and ST-segment elevation.[15]

DIAGNOSIS

In case of renal involvement, the only finding on physical examination that might suggest FMD is a systolic and diastolic murmur in the abdomen or flanks.[1] Doppler ultrasound, computed tomography angiography, and magnetic resonance angiography might be useful in detecting FMD lesions, and should be performed to rule out any of intracranial aneurysms.[16–18]

The diagnosis of FMD is established by histopathology or angiography.[2,11] The latter, in addition to diagnosing, suggests the arterial layer affected, because each arterial layer has a differentiated pattern on the imaging study. Involvement of the media is seen as the classical pattern of "pearl necklace", in which sequential thickening and thinning of the affected arterial segment occurs.[2,19] The carotid and vertebral arteries are affected in their middle and distal portions.[9] While injury to the intima is seen as an image of focal and concentric stenosis, that of the adventitia appears as tubular stenosis on angiography.[3,5]

In addition to those patterns, the arterial wall can be either thinner, due to rupture of the internal elastic lamina, originating an aneurysm, or thickened by dysplastic lesions, originating stenosis, which occurs in 16%–38% of the cases with renal artery involvement. It is worth noting that, when stenosis occurs, occlusion is rarely complete.[1]

TREATMENT

FMD is a progressive disease, requiring periodical angiography for patients' follow-up. Its treatment is still object of discussion,[10] being recommended only in symptomatic cases.[2,10]

The treatment of FMD consists in revascularization,[5] which can be either surgical or via percutaneous transluminal angioplasty (PTA).[2] Intravascular stent placement is the treatment of choice, and has the same success rate of the traditional surgical techniques, but with lower rates of mortality, complications, and restenosis.[5,12] A prospective study involving 27 patients with renal artery FMD that assessed the restenosis rate and

blood pressure response to PTA has reported that 74% of the patients achieved good blood pressure control.[20]

DIFERENTIAL DIAGNOSIS

Vasculitis

DFM can manifest as a systemic vascular disease, mimicking polyarteritis nodosa (PAN) and being called pseudovasculitis. Visceral angiography is an important diagnostic tool, but it lacks specificity. Both vasculitis and FMD can have a severe clinical course, but require different treatments; thus, it is important to recognize the limitations of angiography in the diagnosis of such diseases.[2] FMD is, by definition, a non-inflammatory disease; thus, no inflammatory characteristic is observed, except in cases of associated infarctions. However, the biological signs of inflammation are absent in about one-third of cases of vasculitis.[6]

In vasculitis, vascular stenosis might occur, causing ischemia of the organ or blood vessel injury, and resulting in aneurysm formation or hemorrhage.[21] The diagnosis of vasculitis is usually based on the recognition of characteristic clinical presentation patterns, such as fever, night sweats, malaise, weight loss, arthralgia, and myalgia. The following laboratory findings can occur in some patients: normocytic and normochromic anemia; leukocytosis; thrombocytosis; erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) elevated; and ANCA positivity. Angiography and biopsy should be performed whenever possible.[10,22–24] Histological examination is often considered gold-standard. One characteristic histological image can confirm a diagnosis of vasculitis and exclude other diseases, such as neoplasia and infection. It can also play a role in establishing the cause of the patient's deterioration, especially when the kidneys are affected.[25]

The classification criteria for vasculitis were established in 1990; however, when applied to clinical practice, several initial presentations remain difficult to classify. In such situations, the differential diagnosis should always include pseudovasculitis.[22–24] There are isolate reports of FMD mimicking PAN, Ehlers-Danlos's syndrome, Alport's syndrome, pheochromocytoma, Marfan's syndrome, and Takayasu's arteritis (TA).

PAN and FMD can be diagnosed by angiography, with no histopathological confirmation. This established diagnostic criterion raises the question that the arteriographic profile of those diseases are truly neither pathognomonic nor characteristic. Finding a visceral aneurysm can cause confusion between both diseases.[2]

The clinical characteristics of PAN comprise constitutional symptoms, such as fever and weight loss. The involvement of organs in PAN is represented by arterial hypertension, renal failure, peripheral neuropathy, abdominal pain, and impairment of the musculoskeletal system.[2] Less frequently, cerebrovascular accident and skin involvement (palpable purpura, livedo reticularis, necrotic lesions and infarctions of the finger tips) can occur.[22] The classification criteria comprise clinical and non-clinical elements. Of the later, the discovery of several aneurysmatic dilations up to 1 cm on visceral angiography is considered sufficient for the diagnosis of PAN, even in the absence of histological evidence of the disease, which leads to confusion with FMD.[2] Laboratory tests, such as antinuclear antibodies, rheumatoid factor, and ANCA, are usually negative in PAN, which makes the differential diagnosis even more difficult.[22]

TA and FMD are vaso-occlusive diseases, and the signs and symptoms of both conditions reflect some degree of damage to the extremity of the organ. The presence of inflammation should suggest the diagnosis of TA; however, in the chronic vaso-occlusive phase of the disease, most patients have no inflammatory signs.[26] The American College of Rheumatology diagnostic criteria for TA are as follows: age below 40 years; claudication of the extremities; reduced brachial pulse; blood pressure difference greater than 10 mmHg; subclavian artery or aorta murmur; and angiographic abnormalities. It is worth noting that the classification criteria include no inflammation signs, lacking, thus, specificity.[27] Sometimes only the histopathological exam can differentiate FMD from TA. Although it does not occur in clinical practice, performing three consecutive biopsies increases the diagnostic probability, because the histopathological aspect of both diseases progresses over time; thus, one single assessment can lead to misdiagnosis.[26]

Marfan's syndrome is often the first diagnostic consideration in young patients with ascending aorta aneurysms. Although this is not a frequent site of FMD, in the presence of aneurysms it is always a differential diagnosis. Marfan's syndrome is an hereditary disorder of the connective tissue due to a mutation in the fibrillin-1 gene in chromosome 15. The typical patient is tall and thin, has arachnodactyly and long limbs. The patient's wingspan can exceed his/her height. The upper segment of the body is smaller than the lower segment. In addition, chest deformities, scoliosis, or kyphosis can occur. More than 80% of the patients with Marfan's syndrome have cardiac alterations detected on echocardiography, more commonly mitral regurgitation due to prolapse of the posterior cusp.[28] The differential diagnosis from FMD is facilitated by these characteristic findings.

The implications of this diagnosis are relevant, since the potentially curative treatment can be not performed, while treatment

regimens, such as those with corticosteroids and cytotoxic agents, can be directly and quickly deleterious to the vascular wall, aggravating the lesions.[24] Because the alterations of vasculitis and pseudovasculitis are relatively rare, the physician's lack of familiarity with them can delay the correct diagnosis.[11,22]

Atherosclerosis

Another important differential diagnosis of FMD is atherosclerosis. FMD of the renal arteries is a known cause of secondary hypertension, usually easily differentiated from atherosclerosis of the renal artery, since FMD tends to occur in younger women (under the age of 35 years), at low risk for atherosclerotic cardiovascular disease. FMD of the tibial and fibular arteries has similar symptoms to those of atherosclerosis in the lower limbs. The patients can have intermittent claudication, critical ischemia of the limb, or peripheral microembolism. In the legs, symptomatic FMD can be treated with peripheral angioplasty.[29]

Anticardiolipin antibody syndrome

The association of FMD and carotid artery occlusion has been reported. Clinically, the patient can have features of the antiphospholipid syndrome (APS), such as visual loss, optic atrophy, angina, and recurring strokes. Anticardiolipin antibodies (ACA) are a class of acquired immunoglobulins that bind to a variety of anionic phospholipids and represent a subset of antiendothelial autoantibodies. The association with arterial or venous occlusions is due to their thrombogenic nature. The etiopathogenic relation between ACA and FMD is not clear. Two pathogenic mechanisms have been considered:

- The endothelial lesions in FMD expose the binding sites of antiphospholipid antibodies, inducing their production;
- The interaction of the antibodies with the endothelium would lead to the production of trophic factors, favoring the proliferation of fibroblasts and myoblasts, leading to FMD.[30]

CONCLUSION

The presence of vaso-occlusive conditions in different arterial beds should draw our attention not only to true vasculites, but also to other non-inflammatory conditions that mimic vasculites. Of such conditions, FMD stands out, because it can be a diagnostic challenge, and, when missed, determines inadequate management.

REFERENCES

REFERÊNCIAS

1. Prisant LM, Szerlip HM, Mulloy LL. Fibromuscular dysplasia: an uncommon cause of secondary hypertension. J Clin Hypertens 2006; 8(12):894–8.
2. Siegert CE, Macfarlane JD, Hollander AM, van Kemenade F. Systemic fibromuscular dysplasia masquerading as polyarteritis nodosa. Nephrol Dial Transplant 1996; 11(7):1356–8.
3. Verdure P, Triquenot-Bagan A, Perdu J, Gerardin E, Laquerriere A, Hannequin D *et al*. Dissections artérielles cervicales multiples chez deux frères: dysplasie fibro-musculaire ou maladie du tissu conjonctif? Rev Neurol 2008; 164(S3):F211–5.
4. Rice RD, Armstrong PJ. Brachial artery fibromuscular dysplasia. Ann Vasc Surg 2010; 24(2):255.e1–4.
5. Díaz Rodríguez C, Santos Hernández M, Camacho Cascajo G, García Pérez L, Cao Vilariño M, Tresancos C et al. Infarto renal agudo: complicación de displasia fibromuscular. Hipertensión 2006; 23(2):63–6.
6. la Batide Alanore A, Perdu J, Plouin PF. Dysplasie fibromusculaire artérielle. Presse Med 2007; 36(6 Pt 2):1016–23.
7. Begelman SM, Olin JW. Fibromuscular dysplasia. Curr Opin Rheumatol 2000; 12(1):41–7.
8. Birnbaum LA, Sherry R, Pereira E. Isolated intracranial fibromuscular dysplasia presents as stroke in a 19-year-old female. Arq Neuropsiquiatr 2005; 63(2A):318–20.
9. Poppe AY, Minuk J, Glikstein R, Leventhal M. Fibromuscular dysplasia with carotid artery dissection presenting as an isolated hemianopsia. J Stroke Cerebrovasc Dis 2007; 16(3):130–4.
10. Ortiz-Fandiño J, Terré-Boliart R, Orient-López F, Guevara-Espinosa D, Ramón-Rona S, Bernabeu-Guitart M. Accidente vascular cerebral isquémico secundario a displasia fibromuscular: a propósito de un caso. Angiología 2004; 56(5):505–11.
11. Grau R. Pseudovasculitis: mechanisms of vascular injury and clinical spectrum. Curr Rheumatol Rep 2002; 4(1):83–9.
12. Rouanet A, Javerliat I, Machet MC, Lermusiaux P. Fibrodysplastic popliteal aneurysm and dilatation of pedal artery. Ann Vasc Surg 2009; 23(6):785.e1–4.
13. Mounier-Véhier C, Haulon S, Devos P, Lions C, Jaboureck O, Gaxotte V *et al*. Renal atrophy outcome after revascularization in fibromuscular dysplasia disease. J Endovasc Ther 2002; 9(5):605–13.
14. Rauschka H, Retzl J, Baumhackl U, Bankl HC, Salomonowitz E, Schmidbauer M. Subacute brainstem angioencephalopathy: a case report and review of the literature. J Neurol Sci 2003; 208(1–2):101–4.
15. Ropponen KM, Alafuzoff I. A case of sudden death caused by fibromuscular dysplasia. J Clin Pathol 1999; 52(7):541–2.

16. Herregods N, Beckers R, Van Rattinghe R, Verstraete K. Fibromuscular dysplasia of the carotid artery. JBR-BTR 2008; 91(5):195–7.
17. Shimazaki H. Cerebral infarction attributable to cerebrovascular fibromuscular dysplasia. Brain Nerve 2008; 60(10):1125–33.
18. Benavente L, Calleja S, Fernández JM, Lahoz CH. Fibromuscular dysplasia. Asymptomatic dissection and occlusion of the basilar artery. Neurologia 2008; 23(6):388–91.
19. Watada S, Obara H, Shimoda M, Matsubara K, Matsumoto K, Kitajima M. Multiple aneurysms of the splenic artery caused by fibromuscular dysplasia. Ann Vasc Surg 2009; 23(3):411.e5–7.
20. Birrer M, Do DD, Mahler F, Triller J, Baumgartner I. Treatment of renal artery fibromuscular dysplasia with balloon angioplasty: a prospective follow-up study. Eur J Vasc Endovasc Surg 2002; 23(2):146–52.
21. Langford CA. Vasculitis. J Allergy Clin Immunol 2010; 125(2 Suppl 2): S216–25.
22. Ribi C, Mauget D, Egger JF, Khatchatourian G, Villard J. Pseudovasculitis and corticosteroid therapy. Clin Rheumatol 2005; 24(5):539–43.
23. Suresh E. Diagnostic approach to patients with suspected vasculitis. Postgrad Med J 2006; 82(970):483–8.
24. Jayne D. The diagnosis of vasculitis. Best Pract Res Clin Rheumatol 2009; 23(3):445–53.
25. Miller A, Basu N, Luqmani R. Assessment of systemic vasculitis. Autoimmun Rev 2008; 8(2):170–5.
26. D'Souza SJ, Tsai WS, Silver MM, Chait P, Benson LN, Silverman E *et al*. Diagnosis and management of stenotic aorto-arteriopathy in childhood. J Pediatr 1998; 132(6):1016–22.
27. Marks SD, Tullus K. Do classification criteria of Takayasu arteritis misdiagnose children with fibromuscular dysplasia? Pediatr Nephrol 2010; 25(5):989–90.
28. Shepherd RF, Rooke T. Uncommon arteriopathies: what the vascular surgeon needs to know. Semin Vasc Surg 2003; 16(3):240–51.
29. Chin A, Ntsekhe M. Concomitant renal and iliac fibromuscular dysplasia. Catheter Cardiovasc Interv 2009; 73(4):519–20.
30. Tripathi M, Santosh V, Nagaraj D, Cristhopher R, Chandra PS, Shankar SK. Stroke in a young man with fibromuscular dysplasia of the cranial vessels with anticardiolipin antibodies: a case report. Neurol Sci 2001; 22(1):31–5.