Arteries of fibromuscular dysplasia tell a sympathetic story

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The dangerous arteriopathy fibromuscular dysplasia (FMD) causes strokes, aneurysms, and dissections, primarily in young or perimenopausal women. Hormonal exposure is a potential risk.[1] A small fraction of patients report FMD in another family member, and genetic polymorphisms (loci *PHACTR1*, *LRP1*, *ATP2B1*, and *LIMA1*) are associated with some cases in genome-wide analysis.[2] Still, the origin question of FMD has not been solved.

FMD involves the extracranial internal carotid and renal arteries more often than it does the vertebral, coronary, mesenteric, or medium-size arteries of the extremities.[3] This standout anatomic favoritism for carotid and renal arteries is a second riddle that has not been explained.

"Singularity is almost invariably a clue," said Sherlock Holmes. I am a typical internist, drawn in by mysteries. What singles out the arteries of FMD and, most notably, the renal and internal carotid arteries? I ruminated on this question, and I have a theory. Possibly, it is the intense connection these arteries have to the sympathetic vascular nerves.

The renal and carotid arteries are critical flow regulation instruments. Sympathetic nerves along the carotid arteries regulate cerebral blood flow.[4] So dense is this nerve—artery connection, internal carotid dissections characteristically result in Horner's "ptosis, miosis, and anhidrosis" due to disruption of sympathetic fibers. The sympathetic nerves in the renal arteries govern urine flow and renin release. The renal sympathetic nerves activate with centralized fight-or-flight discharges; however, they are additionally locally activated in response to hydrostatic pressure in the renal pelvis: the "reno-renal reflex."[5] Localized, specialized neural reflexes that govern compartment pressure in the brain[4] and kidneys[5] can turn the renal and carotid arteries into vascular nerve "hot spots" relative to other arteries.

Anatomically, there is an interface between all the arteries of FMD and the sympathetic nervous system (SNS; Fig 1). Along the length of middle-size arteries, post-ganglionic sympathetic fibers form lattices, penetrate into the adventitia, and travel distally. Sympathetic nerves are "dance partners" with these arteries.

Could sympathetic nervous activity be key to the mechanism of FMD?

VASCULAR MATRIX

Vascular nerves are unique. Instead of having one neuroeffector junction or synapse, they have many varicosities along their axons[6] (Fig 2). Each varicosity releases norepinephrine. Without a structural synapse, norepinephrine is not immediately reabsorbed and, thus, diffuses within the matrix.

FMD involves "string-of-beads" dilatations, hypermuscular segments, and collagen.[3] This transformation is noninflammatory but not acellular. Perhaps FMD begins with the following sequence. An unrelated pathology activates the SNS. At sympathetic varicosities, norepinephrine activates fibroblasts. Fibroblasts promote smooth muscle proliferation and transform to myofibroblasts, depositing collagen. Activated mast cells and, possibly, the cytokine transforming growth factor-beta (TGF-β) promote transformation and migration of myofibroblasts to the media and intima.[3,7] This sequence could promote remodeling, particularly if incessant sympathetic signaling were paired with TGF-β or with exaggerated mast cell activation. Intriguingly, circulating TGF-β is increased in FMD.[3]

SYMPATHETIC STORMING

In health, normal sympathetic surges are closely modulated and partially extinguished by inhibitory tracts. These tracts descend through the hypothalamus, brainstem, and spinal cord, quieting sympathetic preganglionic neurons in the spinal cord. Although many chronic illnesses can modestly activate sympathetic nerves, brain and spinal conditions can massively activate the SNS by disabling central inhibition. This can occur in paroxysmal sympathetic hyperactivity ("sympathetic storming"),[8] as is seen with traumatic brain injury, hydrocephalus, and/or a cerebrospinal fluid (CSF) leak. Sympathetic hyperexcitation also occurs with disturbances at the skull base and with spinal cord injury ("autonomic dysreflexia"). Autonomic dysreflexia can result from trauma, radiation, degenerative myelopathy, cervical instability, Chiari malformation, syringomyelia, tethered cord, and multiple sclerosis.[9]

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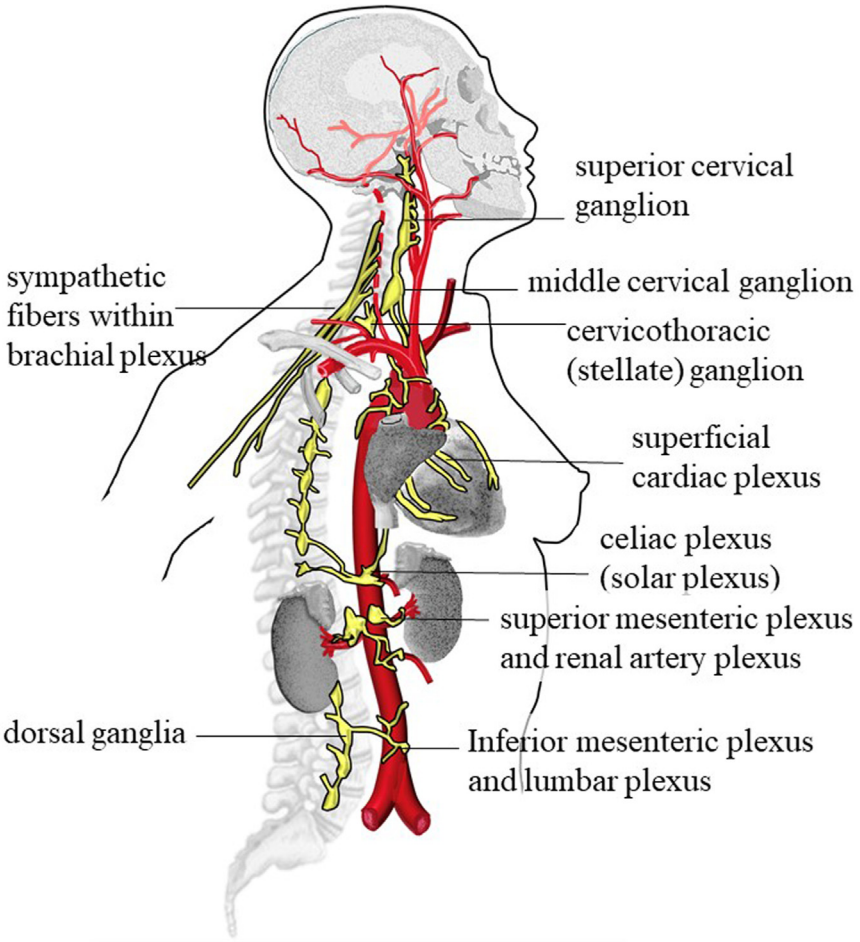

Fig 1. Schematic of major sympathetic ganglia and major arteries. Sympathetic fibers exit the spinal cord at T1 to L2 and travel locally, cephalad, or caudally to synapse in ganglia. Major ganglia of the sympathetic nervous system (SNS) and post-ganglionic sympathetic fibers overlie the middle-size arteries that are affected in fibromuscular dysplasia (FMD). The heart and spine illustrations were modified and incorporated with permission from BioDigital and Globus Medical.

Diseases with disinhibited sympathetic activity should be of interest in FMD.

Several of these conditions are challenging to recognize, have symptom overlap with FMD, and would not be diagnosed without specialized imaging. In FMD, spinal disease is unexpectedly prevalent.[1,3] In one FMD study, 47 patients underwent full spine magnetic resonance imaging.[3] The findings were striking: 6% had Chiari I malformation, 15% had cerebellar tonsillar ectopia (which can be seen in Chiari variants or CSF leak), and 42% displayed dural ectasia (a predisposing factor to CSF leak). In addition, cervical stenosis, arthritis, and scoliosis were unusually prevalent.[3]

AUTONOMIC SYMPTOMS

Dysautonomia can cause hypertension, headaches, orthostatic heart rate changes, insomnia, sweats, neck pain, visual blurring, ptosis, fatigue, ringing tinnitus, and pulsatile tinnitus. All these symptoms are common in FMD. Traditionally, FMD symptoms have been attributed to narrowed arteries; however, these are not stereotypical symptoms of hypoperfusion. It would be better to describe the FMD symptom cluster as autonomic. Consider what we see outside of FMD. In preeclampsia and idiopathic intracranial hypertension, two distinct conditions known to cause sympathetic hyperactivity, patients experience the same system cluster of headaches, visual blurring, pulsatile tinnitus, hypertension, back pain, and neck pain. In essence, ongoing symptoms in FMD might not arise from individual arteries but, instead, might indicate background, centrally originating dysautonomia.

DISCUSSION

This year, I have observed carotid–vertebral FMD in a woman concurrently diagnosed with Chiari malformation and carotid–vertebral FMD in a patient being treated for hydrocephalus. This second patient also has

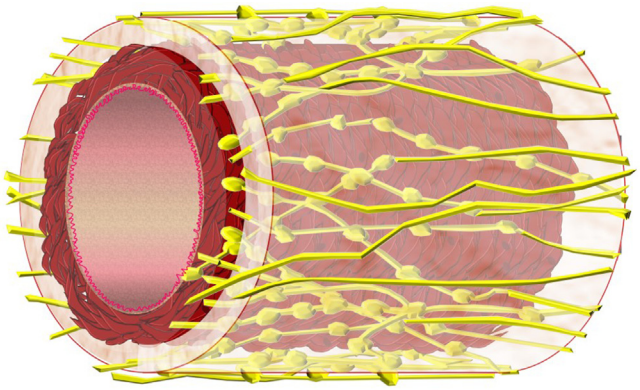

Fig 2. Sympathetic vascular nerves web the surface of muscular arteries and penetrate the tunica adventitia. Instead of having one neuroeffector junction or synapse, post-ganglionic sympathetic vascular nerves have many axonal varicosities, and each varicosity releases norepinephrine. Somatic afferent nerves (not shown) interact with sympathetic vascular nerves, locally augmenting norepinephrine release. Fibroblasts and mast cells (not shown) are also abundant in the adventitia, held in a loose connective tissue matrix.

brachial FMD in an injured arm with complex regional pain syndrome (a dysautonomia previously named "reflex sympathetic dystrophy"). Are these illnesses unrelated or related?

Pathologically augmented SNS activity might promote FMD, which is currently an unexplained arteriopathy. Emerging hereditary risks are still relevant. However, in this sympathetic story, FMD could be a secondary disease in some patients, not a primary condition.

There are gaps to consider. The phenomenon of arterial "beading" is not addressed. Sympathetically innervated precapillary arterioles are rarely involved; possibly, these smaller arteries lack a large enough matrix interstitium to retain norepinephrine, limiting the fibroblast response. FMD is not hypercellular; however, changes mediated by mast cells occur mostly through cytokines. This model does not explain why close to 90% of FMD cases occur in women,[1,3] although menopausal autonomic dysregulation[10] and sex differences in mast cell activity could be relevant.

Patients with symptomatic FMD should be evaluated for underlying conditions that might provoke sustained autonomic imbalance. This could require specialized imaging of the brain and spine and targeted consultation. Consideration of a neurally triggered origin of FMD might lead to a widened understanding of FMD and identification of treatable underlying conditions.

DISCLOSURES

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