FIRST INTERNATIONAL CONSENSUS ON THE DIAGNOSIS AND MANAGEMENT OF FIBROMUSCULAR DYSPLASIA

Short title: International Consensus on Fibromuscular Dysplasia

Online Supplemental Material

Emerging biomarkers and future directions

Ultrasound echo tracking and the "triple signal"

Increasing evidence from large registries has established that FMD is a systemic disease, with a very high prevalence of multiple arterial bed involvement (1). The consolidation of this knowledge opens new perspectives for the FMD clinical work-up, through the exploration of easily accessible, but usually not affected arterial beds. In patients with renal multifocal FMD, Boutouyrie et al. showed an intermediate vascular phenotype, called the "triple signal", detectable by echo tracking (ultrasound) techniques at arterial sites distant from the clinical manifestation of FMD, such as the radial and common carotid arteries(2). The "triple signal" consists of a supernumerary echogenic interface, visible on both grayscale and on radiofrequency-based ultrasound images, located between the blood–intima and the media–adventitia interfaces, which may correspond to medial hyperplasia (2,3). The "triple signal" has also been reported in first-degree relatives of index cases and the findings are consistent with the possibility of autosomal dominant transmission (2).

A preliminary analysis from the MEDYA (MEcanismes physiopathologiques de la DYsplasie fibromusculaire Arterielle, ClinicalTrials.gov Identifier: NCT01935752) study, a cross-sectional

study aimed at exploring vascular pathophysiological mechanisms of FMD, confirmed that the "triple signal" is strongly associated with carotid remodeling (i.e. increased intima-media thickness) and suggest a possible association with altered mechanical properties (4). However, the "triple signal" was also present in individuals with essential hypertension, another condition characterized by medial hypertrophy (4). Ongoing analysis of these data, including microRNA and microvesicle assessment together with vascular function testing, will better clarify whether endothelial and smooth cell dysfunction are involved in the pathophysiology of FMD.

Ultra-high resolution ultrasound of the artery wall

The study of non-affected and easily accessible medium and small-sized arteries, such as the radial artery, has been recently made possible by the commercial availability of ultra-high frequency ultrasound for human use. The radial arteries have diameter and histology similar to that of arteries commonly affected by FMD (e.g., renal and carotid/vertebral arteries). Preliminary results by Bruno et al. confirmed an increased radial wall thickness in patients with FMD in comparison to healthy controls. Most strikingly, wall ultrastructure appeared subverted and characterized by greater inhomogeneity of the echogenic layers (5). Interestingly, similar alterations were found among patients with a history of SCAD (6). However, these preliminary results need to be replicated in larger, independent cohorts of patients with FMD. Furthermore, the anatomical correlates of radial artery disarray in FMD need to be fully clarified.

Fibroblast-based investigation

At a more molecular and genetic level, the DEFINE FMD study (Defining the Basis of Fibromuscular Dysplasia; ClinicalTrials.gov Identifier: NCT01967511), that has recruited >300

subjects and with a target enrollment of 600, has 3 objectives including: (1) to establish a library of fibroblasts, DNA, plasma and serum from patients with FMD, SCAD, and CeAD and healthy controls, (2) to perform a fully powered cross-tissue systems analysis of the key regulatory gene networks and disease drivers underlying FMD, SCAD, and CeAD and, (3) to cross-compare the molecular and genomic profiles of FMD, SCAD, and CeAD to establish the degree of biologic similarity among these disorders. DEFINE FMD is founded upon the fact that fibroblasts, which are known to be abnormal in FMD patients, can be obtained by dermal (skin) biopsy (7). Dermal fibroblasts have been used with success to study other vascular disorders and the investigators are undertaking high-throughput sequencing techniques to profile these cells in diseased versus healthy matched controls (8). Notably, a clear challenge is that fibroblast cell lines must be individually isolated and meticulously handled for every subject – a costly and labor-intensive undertaking. Nevertheless, this systems genetics approach has been highly informative for coronary artery disease and other disorders, and when mature, the DEFINE FMD study promises to be a valuable resource for understanding FMD (9-11).

Referenfces

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