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Primary media sclerosis Mönckeberg: Diagnostic criteria

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SOUHRN

Mönckebergova (mediální) skleróza je spojena s progredující kalcifikací medie stěny tepen, přičemž intima zůstává nedotčena. Toto onemocnění je často spojeno s diabetem 2. typu a s chronickým onemocněním ledvin. V některých případech však nejsou známy žádné rizikové faktory, z čehož lze usuzovat na primární dystrofickou kalcifikaci. V tomto článku navrhujeme diagnostická kritéria a přimlouváme se za cílený výzkum zaměřený na toto dosud nedostatečně popsané cévní postižení.

Keywords:
Diagnostics
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ABSTRACT

Media sclerosis Mönckeberg (MSM) is associated with progressive calcifications of the arterial wall media leaving the intima intact. MSM is frequently associated with type 2 diabetes mellitus and chronic kidney disease. In some cases, however, no risk factors are present suggesting presence of a primary dystopic calcification disorder. Here we propose diagnostic criteria and advocate dedicated research into this as yet poorly defined vascular disorder.

Introduction

The clinical relevance of media sclerosis Mönckeberg (MSM) relates largely to three major issues. First, stiffening of the large conducting arteries increases the workload of the heart and may contribute to heart failure in the long run [1,2]. Second, calcification of the micro-vessels [3] may impair blood pressure regulation and organ perfusion. Third, MSM if associated with atherosclerosis may interfere with compensatory remodeling of the arterial walls [4] and may accelerate the stenotic phase of the disease.

MSM is characterized by progressive deposition of largely crystalline hydroxyapatite within the vascular smooth muscle cells and intercellular matrix of the media. While passive precipitation of calcium phosphate driven by physico-chemical forces has been favored in the past more recently active biological process akin to bone ossification has been favored [5]. However, regardless of the nature of the driving process [6] disturbances of the phosphate metabolism characterized by the disequilibrium between the inorganic phosphate (Pi) and pyrophosphate (PPi) have been recently favored to represent the final common pathway [7].

MSM occurs predominantly in patients with type 2 diabetes mellitus and chronic kidney disease [8–10]. However, in addition also MSM without any known risk factors for vascular calcifications has been reported [11], possibly suggesting a primary disorder of intra-extracellular handling

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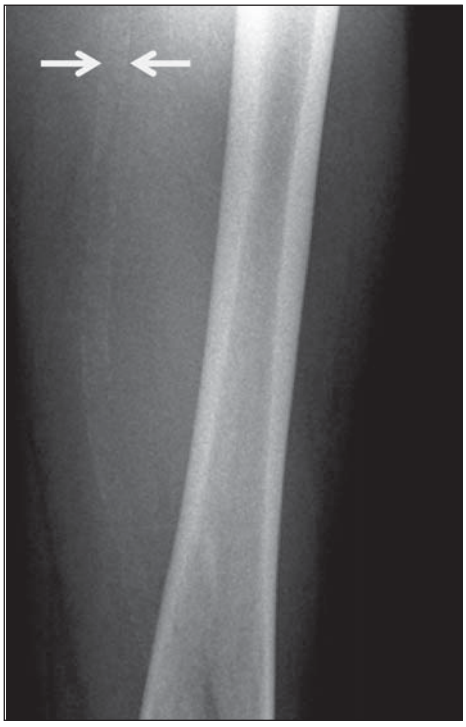

Fig. 1 – Media sclerosis. Native x-ray radiograph shows a typical "railroad track" pattern of calcification in the entire course of the superficial femoral artery (arrows).

of the phosphate species. To allow distinction between the common secondary and the less frequent primary type of MSM diagnostic criteria for the primary form are suggested.

Diagnostic criteria of MSM

In clinical settings media sclerosis is frequently identified accidentally from conventional x-ray radiographs of pelvis or lower extremities performed in the course of an unrelated diagnostic work-up or angiographic studies in patients with peripheral artery disease. On x-ray radiography of pelvis or lower extremities media sclerosis is visualized as more or less uniform linear radiopaque "railroad tracks" (Fig. 1) [12,13]. With progressing disease granulations become coarser and less regular.

In patients evaluated by ankle-brachial index (ABI) measurements values ≥1.1 are suggestive of MSM; readings of 1.1–1.3, 1.3–1.5, and >1.5 have been proposed to denote an early, intermediate and late media sclerosis, respectively [14]. In patients with ankle-brachial index ≥1.1 the toe-brachial index has been proposed to improve the specificity of segmental blood pressure measurements [15]. However, the role of the toe-brachial index in diagnostics of media sclerosis remains uncertain [16]. Nevertheless, despite limitations ankle-brachial index remains the most important screening tool for MSM.

On vascular ultrasound B-mode images MSM is recognized by distinct echogenic spotting beneath the intact intima. In more advanced stages echogenic sites become more numerous providing the appearance of "string of beads" located in the abluminal layer of the arterial walls. In late stages finally continuous layers of echogenic signals are seen (Fig. 2). However, due to the frequent co-incidence of MSM and atherosclerosis the distinct ultrasonic pattern of media sclerosis can be discounted in routine examinations in clinical settings.

Table 1 – Criteria to establish the diagnosis of MSM.
Visualization of abluminal calcifications underneath intact intima (native x-ray, ultrasound, IVUS or OCT)
And Ankle-brachial index ≥1.1
Or Pulse wave velocity >10 m/s

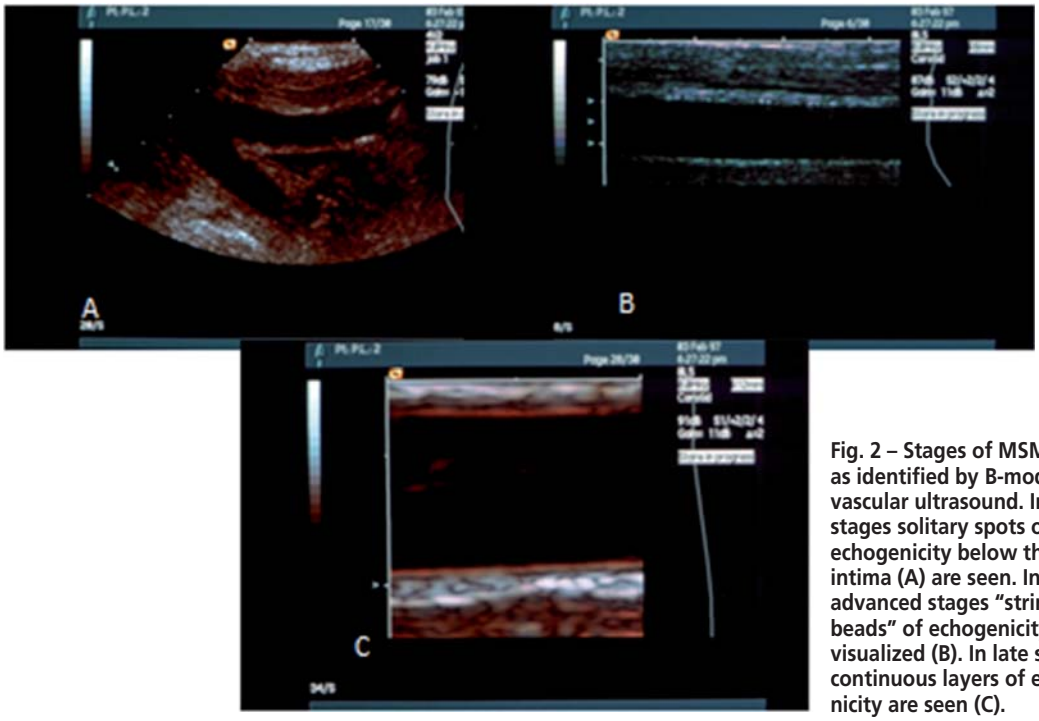

Fig. 2 – Stages of MSM as identified by B-mode vascular ultrasound. In early stages solitary spots of high echogenicity below the intima (A) are seen. In more advanced stages "strings of beads" of echogenicity are visualized (B). In late stages continuous layers of echogenicity are seen (C).

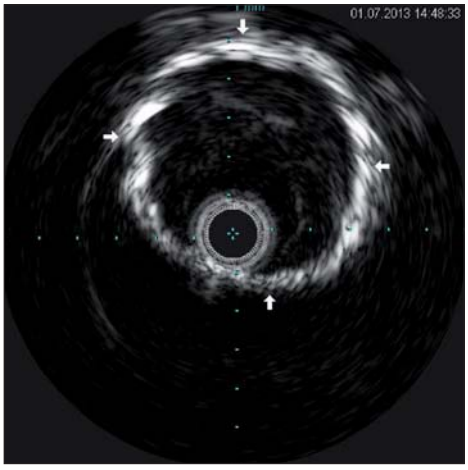

Fig. 3 – Intravascular ultrasound image showing four quadrant calcification of the superficial femoral artery in a patient with media sclerosis (courtesy Prof. Zeller, Bad Krozingen).

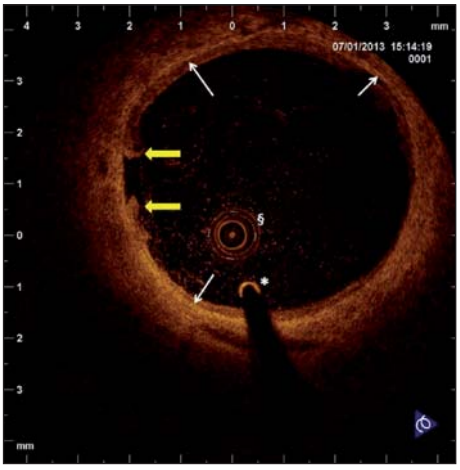

Fig. 4 – Media sclerosis is seen as calcified more or less continuous layer within the media (white arrows) employing optical coherence tomography. In this patient with media sclerosis also an intimal tear of an atherosclerotic lesion is visualized (yellow arrows); §, * denote the imaging catheter (courtesy Prof. Zeller, Bad Krozingen).

Table 2 – Exclusion criteria for secondary MSM; the values are laboratory specific.

Disorder	Laboratory data
Diabetes mellitus type 2	Fasting glucose ≥126 mg/dL (2×) or HbA_{1c} ≥7% or postprandial glucose >198 mg/dL
Chronic renal disease	Glomerular filtration rate ≥90ml/min*; albumin excretion in urine <2 mg/l or <80 mg/24 h
Parathyroid gland disorders	Parathyroid hormone <10–55 picogram/milliliter (pg/mL)
Vitamin D disorders	25-hydroxyvitamin D <20 ng/mL (50 nmol/l) and level between 21–29 ng/mL (52.5–72.5 nmol/l, respectively); 1,25-dihydroxyvitamin D: <20 or 45 pg/ml (<48 or >108 pmol/L)
Electrolyte disorders	Calcium (total) [<8.5 or >10.2 mg/dL], phosphorus [<2.4 or >4.1 milligrams per deciliter (mg/dL)], magnesium [<1.8 or >3.6 mg/dL]
Intake of vitamin K-antagonists	

* Cockcroft-Gault-formula.

In patients undergoing endovascular interventions media sclerosis may be visualized employing intravascular ultrasound (IVUS) or optical coherence tomography (OCT). On IVUS media sclerosis is seen as highly echogenic zones located within the media. Due to the presence of fibrotic tissue typically no acoustic "shadowing" is seen in contrast to calcifications associated with atherosclerosis (Fig. 3).

Compared to IVUS OCT provides higher resolution und substantially better visualization of the innermost layers of arterial walls (Fig. 4).

Laboratory evaluations of biomarkers specific for VC such as inorganic phosphate, fibroblast growth factor 23 (FGF23), OPN, OPG, MGP, fetuin-A, alkaline phosphatase and interleukin-6 (IL-6) have produced negative or equivocal results [17] and have not yet been standardized for routine clinical use.

Primary media sclerosis Mönckeberg: proposed diagnostic criteria

Primary MSM features morphologic phenotype of the common type associated with type II diabetes or chronic renal disease. Thus, the diagnosis of the primary MSM requires the documentation of typical findings on native x-ray images, B-mode ultrasound, IVUS or OCT that are associated ABI ≥1.1 and or pulse wave velocity >10 m/s (Table 1). To establish the diagnosis of the primary MSM secondary causes such as diabetes mellitus type 2, chronic kidney disease, disorders of the bone metabolism, disorders of the calcium, phosphate and magnesium metabolism need to be excluded (Table 2).

Discussion

Lacking the typical known risk factors the primary MSM likely represents distinct biological entity; only a single case has been reported in the literature to date [11], yet it appears to be far more common in the real-life day to day medicine. To allow clinical diagnosis of primary MSM the set of criteria confirming the presence of MSM and excluding the known risk factors for vascular calcifications have been proposed. Because of the likely irreversible nature of calcifications associated with the primary and secondary MSM prevention and early detection represent

the key targets of diagnostics. Albeit recent evidence points towards the causal relationships between accumulating hydroxyapatite deposits and disturbances in handling of inorganic phosphate and pyrophosphate groups by vascular smooth muscle cells [18] this appealing link still awaits definite confirmation. To date, no biological indicators of the presence of MSM have been established, albeit the rise in osteoprotegerin (OPG), a glycoprotein participating in inflammatory response modulation, appears to correlate with the progression of vascular calcifications in a selected group of patients with chronic renal disease [19]. Focusing clinical attention onto this important disease entity may reveal not only the true incidence of primary MSM in common populations but also redirect research into the molecular biology of vascular calcifications associated with the primary MSM.

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