Nutrition, Metabolism & Cardiovascular Diseases (2012) 22, 393–399

Available online at www.sciencedirect.com

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Nutrition, Metabolism & Cardiovascular Diseases

REVIEW

Primary mitochondrial arteriopathy

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Received 4 October 2011; received in revised form 27 December 2011; accepted 5 January 2012

KEYWORDS
Arterial;
Vessel;
Vascular;
Pathology;
Perfusion;
Metabolic disease;
Cytopathy;
Mitochondrial

Abstract *Aim:* Whether arteries are affected in mitochondrial disorders (MIDs) was under debate for years but meanwhile there are strong indications that large and small arteries are primarily or secondarily affected in MIDs.
Data synthesis: When reviewing the literature for appropriate studies it turned out that vascular involvement in MIDs includes primary or secondary micro- or macroangiopathy of the cerebral, cervical, and retinal arteries, the aorta, the iliac arteries, the brachial arteries, or the muscular arteries. Arteriopathy in MIDs manifests as atherosclerosis, stenosis, occlusion, dissection, ectasia, aneurysm formation, or arteriovenous malformation. Direct evidence for primary cerebral microangiopathy comes from histological studies and indirect evidence from imaging and perfusion studies of the brain. Microangiopathy of the retina is highly prevalent in Leber's hereditary optic neuropathy. Macroangiopathy of the carotid arteries may be complicated by stroke. Arteriopathy of the aorta may result in ectasia, aneurysm formation, or even rupture. Further evidence for arteriopathy in MIDs comes from the frequent association of migraine with MIDs and the occurrence of premature atherosclerosis in MID patients without classical risk factors.
Conclusions: Mitochondrial arteriopathy most frequently concerns the cerebral arteries and may result from the underlying metabolic defect or secondary from associated vascular risk factors. Vascular involvement in MIDs has a strong impact on the prognosis and outcome of these patients.

Abbreviations: ADC, Apparent-diffusion coefficient; AVM, Arteriovenous malformation; CADASIL, Cerebral autosomal dominant arteriopathy with stroke and ischemic leucencephalopathy; COX, Cytochrome-C-oxidase; PEO, Progressive external ophthalmoplegia; DWI, Diffusion-weighted imaging; FMD, Flow-mediated vasodilation; LHON, Leber's hereditary optic neuropathy; MELAS, Mitochondrial encephalopathy, lactic acidosis and stroke-like episodes; MERRF, Myoclonus epilepsy with ragged-red fibres; MID, Mitochondrial disorder; MIDD, Maternally inherited diabetes and deafness; mtDNA, Mitochondrial DNA; nDNA, Nuclear DNA; SDH, Succinat dehydrogenase; SLE, Stroke-like episode; SLL, Stroke-like lesion; SPECT, Single photon emission computed tomography; SSV, Strongly-succinate dehydrogenase-reactive vessels; VSMC, Vascular smooth muscle cell.

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doi:10.1016/j.numecd.2012.01.002

Introduction

Since the first description of stroke-like episodes (SLEs) in patients with mitochondrial encephalopathy, lactacidosis and stroke-like episodes (MELAS) syndrome it is under debate whether or not arteries are involved in the pathogenesis of SLEs [1]. It is also unclear whether arteries are generally affected or not by the metabolic defect causing a mitochondrial disorder (MID). During recent years, however, a number of indications have been provided revealing that there is indeed involvement of small or large arteries of various organs in various MIDs. The following review aims at summarizing and discussing recent findings concerning the primary affection and involvement of arteries in MIDs. Table 1

Types of arteriopathy in MIDs

Generally, arteriopathy in MIDs may be primary or secondary. Primary mitochondrial arteriopathy is due to affection of arterial structures (endothelium, muscularis, adventitia, pericytes (connective tissue cell that covers endothelial cells to form a capillary)) by the underlying metabolic defect, resulting in the destruction of the vessel wall (primary atherosclerosis) consecutive stenosis, occlusion, dissection. rupture, or aneurysm formation. Secondary arteriopathy in MIDs may result from risk factors for atherosclerosis, such as diabetes, hyperlipidemia, or arterial hypertension, which are frequently found in MIDs and are the cause of secondary atherosclerosis in these patients. Secondary arteriopathy may accompany primary arteriopathy why it is often difficult to distinguish between these entities. Aneurysm formation in MID patients with arterial hypertension may be another secondary arteriopathy in MIDs. Secondary arteriopathies were not the topic of this review.

Location of mitochondrial arteriopathy

In primary as well as secondary mitochondrial arteriopathy small (microangiopathy) or large arteries (macroangiopathy) may be affected. There is direct and indirect evidence that the microangiopathy in MIDs is more prevalent than macroangiopathy but no systematic studies on this matter are available so far. Affected arteries in mitochondrial arteriopathy may be the intra-cerebral arteries, the extracranial arteries, the retinal arteries, the aorta, the iliac arteries, the brachial arteries, or arteries of the skeletal muscle. Among these, mitochondrial arteriopathy most frequently affects the intra-cerebral arteries and the intra-muscular arteries but generally all vascular beds may be affected.

Primary mitochondrial arteriopathy of the cerebral arteries

Direct evidence

In a 14yo boy with non-syndromic MID cerebral biopsy revealed spongiform changes, swollen endothelial cells,

Table 1 Human MIDs in which primary arteriopathy has been reported.

Affected arteries	Pathology	MID	Reference
Cerebral arteries	Zytotoxic edema in SLL	MELAS	[8]
	Decreased blood flow in SLL	MELAS	[12]
	Hypo/hyperperfusion in SLL	MELAS	[11]
	Hypoperfusion in SLL	MELAS, PEO	[13]
	Microangiopathy	ETHE1	[15]
	Capillary shunting	Leigh syndrome	[9]
	Ischemic stroke	CIV-defect	[41]
	Migraine-like headache	MELAS	[42]
	Decreased CO_2 reactivity	MELAS	[14]
	Swollen endothel, mitochondria ↑	NSMID	[2]
	Microangiopathy	MELAS	[3]
	High COX-deficiency Increased heteroplasmy	MELAS	[4]
Retinal arteries	Peripapillary tortuosity, ectasia	LHON	[16,17,18,19,20]
Cochlear arteries	Affection of stria vascularis	MELAS	[22]
Extracranial arteries	Dissection	NSMID	[23]
	Carotid artery occlusion	NSMID	[6]
Brachial arteries	Endothelial dysfunction	MELAS	[11]
Aorta	Rupture	MELAS	[25]
	Dilation of aortic root	NSMID	[24]
Iliac arteries	Leriche syndrome	NSMID	[26]
Muscle	SVV	MELAS	[7,11,12,28,29,30,31,32,33,34,35]
	Abnormal mitochondria ↑ in endothelial and VSMC	MELAS	[12,36]
	Oxidative/nitrative stress↑	NSMID	[37]
Skin	Abnormal endothelial mitochondria	MELAS	[43]

NDMID: non-syndromic MID, VSMC: vascular smooth muscle cells, SVV: strongly-succinate dehydrogenase-reactive vessels.