Vasculopathy in mitochondrial disorders

Josef Finsterer, MD, PhD

Abstract - Objectives: Mitochondrial disorders (MIDs) are usually multisystem diseases and may manifest in addition to other systems also in the vasculature. Direct evidence for microangiopathy in MIDs derives from the following findings: histologically confirmed generalised microangiopathy in MELAS patients; increased mtDNA mutation load in leptomeningeal and cortical vessels of MELAS patients; strongly SDH-reactive blood vessels on muscle biopsy in MELAS- and MERRF-patients; swollen endothelial cells in MERRF-patients. Findings indicating macroangiopathy include: dilation of the aorta in MID patients; aortic rupture in MELAS-patients; spontaneous cerebral artery dissection in MELAS-patients; transient occlusion of internal carotid artery in MID-patients; or high prevalence of premature atherosclerosis in MID-patients. Indirect evidence for vasculopathy in MIDs derives from findings like: stroke-like lesions, which also contain areas of cytotoxic edema; decreased cerebral perfusion on SPECT and perfusion-CT in MELAS-patients; migraine frequently associated with MID; CADASIL-patients, which develop features of MID and carry mtDNA mutations; impaired CO2 reactivity of intracerebral arteries in MID-patients; or reduced flow-mediated vasodilation due to altered NO-generation. Conclusion: Endothelial cells or smooth muscle cells of large or small arteries may be affected in MIDs. Arteriopathy in MIDs contributes significantly to the course and outcome in these patients and is often the cause of premature morbidity or mortality.

Key words - angiopathy, vasculopathy, arteriopathy, vessel disease, smooth muscle, mitochondrial disorder, respiratory chain, genetics

I. INTRODUCTION

Mitochondrial disorders (MIDs) are either multisystem conditions at onset or become such during the disease course in the majority of the cases. Though the peripheral nervous system is the one most frequently involved, affection of other systems contributes to the variable phenotype of MIDs. Since the first descriptions of MIDs there is increasing evidence that the vasculature, in particular the smooth muscle cells of the arterial walls and endothelial cells, are frequently affected [1]. Recent finding support the notion that there is a mitochondrial arteriopathy due to impaired provision of energy or increased oxidative or nitric stress. Evidence for affection of the arterial walls in MIDs derives from a number of findings and may be either direct or indirect. Arteriopathy in MIDs may manifest as microangiopathy, macroangiopathy, or both.

II. METHODS

A literature search via Pubmed (www.ncbi.nlm.nih.gov/sites/entrez?db=pubmed) using the search terms “vasculopathy”, “angiopathy”, “arteriopathy”, “endothelium”, “vessels”, “vascular”, “mitochondrial disorder”, “MELAS”, “MERRF”, “Kearns-Sayre syndrome”, “Leigh syndrome” and “stroke-like episode” alone or in combination was carried out and the appropriate papers searched for studies dealing with the topic. Reference lists of each of the appropriate papers were further searched for further leads.

III. RESULTS & DISCUSSION

A. Direct evidence for arteriopathy in MIDs

a) Microangiopathy

The first indication for arteriopathy was provided by studies, which found that there is microangiopathy in MIDs [2,3]. In a 13yo mitochondrial encephalopathy lactic acidosis and stroke-like-episode (MELAS) patient with a complex IV defect, stroke-like episodes, myopathy and cardiomyopathy, autopsy revealed generalised mitochondrial microangiopathy [2]. In a study on brains from two patients with MELAS syndrome there were only few cytochrome-C-oxidase (COX) negative neurons in all cerebral regions but the most severe COX-deficiency and the highest proportion of the m.3243A>G mutation was found in walls of leptomeningeal and cortical vessels, suggesting that microangiopathy may contribute to the pathogenesis of a stroke-like-lesion [4]. A third strong direct evidence for microangiopathy in MIDs comes from the finding that muscle biopsy particularly in MELAS syndrome and myoclonus epilepsy with ragged-red fibers (MERRF) patients may show succinat-dehydrogenase (SDH) hyper-reactivity of smooth muscle cells of arterioles (strongly SDH-reactive blood vessels (SSV)) [5,6,7,8,9,10,11]. SDH-hyper-reactivity in these patients indicates dysfunction of mitochondria [12]. In a study on five MERRF-patients typical SSV fibers, which were negative for COX, were found [8]. Microangiopathy in the muscle was also found in another family with MERRF syndrome [5]. In these patients the morphology of mitochondria in smooth muscle cells of arterioles was abnormal [5]. Biopsies of cerebral tissue from another study showed vascular lesions in the sense of swollen endothelial cells [13]. In
MELAS patients, on the contrary, SSV fibers had normal COX activity [8]. In a study on 11 patients with CPEO, only two SSV blood vessels were found among 69 vessels studied [7].

b) Macroangiopathy

Indication for macroangiopathy in MIDs was provided by a study on ten patients with a MID showing dilation (aneurysm) of the aorta in all of them [14]. The underlying pathomechanism resulting in aortic dilation remained unclear as well as the long-term consequences of this observation. However, recent findings explain abdominal aortic aneurysm formation by mitochondrial-dependent apoptosis of smooth muscle cells, macrophages, and neutrophils, as evidenced by transmission electron microscopy and the TdT-mediated dUTP-biotin nick end labelling (TUNEL) method in elastase-perfused aortic aneurysms [15]. Evidence for macroangiopathy in MIDs was also provided by a recent report about a single patient with aortic rupture in whom the event was attributed to vasculopathy from the underlying MELAS syndrome [16]. In this patient there was marked disarray of the smooth muscle architecture of the aorta and uniformly decreased COX-staining of endothelial and smooth muscle cells of the aorta and the vasa vasorum [16]. The heteroplasmy rate of the pathogenic mutations in the affected arteries was high. Recently, there have been also reports showing cerebral artery dissection as a manifestation of the mitochondrial arteriopathy [17]. In three males with MELAS syndrome spontaneous dissection of the internal carotid artery occurred in two and of the posterior cerebral artery in one, all resulting in ischemic stroke [17]. Macroangiopathy was also found in a patient with MID due to a rRNA(Pha) mutation and recurrent embolic strokes due to transient occlusion of the internal carotid artery, the middle cerebral artery, or the anterior cerebral artery [18]. Strokes were assumed to have been caused by artery-to-artery embolism from the internal carotid artery into the median cerebral artery and anterior cerebral artery [18]. A further strong argument for a vasculopathy in patients with a MID is the finding that atherosclerosis may be more prevalent and premature in these patients [19]. In a female with MELAS syndrome premature atherosclerosis of the large cerebral arteries was found on clinical and pathoanatomic investigations [19]. Contrary to other reports about MELAS patients, there was no indication for microangiopathy in the cerebrum or retina [19]. Severe atherosclerosis in the absence of classical risk factors for atherosclerosis has been also described in a 54-ya old patient with Leriche-syndrome who was suspected to suffer from an MID based upon easy fatigability, exercise intolerance, myoglobinurea, recurrent creatine-kinase elevation, abnormal lactate stress testing, muscle biopsy indicative of metabolic myopathy, and abnormal MR-spectroscopy [20]. Since classical risk factors were absent in this patient and no other causes were found which could explain severe atherosclerosis, the vascular pathology was attributed to the mitochondrial disorder. Extremely narrowed internal carotid arteries and basilar artery (Moya-Moya appearance) with multiple collaterals were found in two siblings with suspected MID presenting with seizures, stroke-like lesions, pulmonary hypertension, arterial hypertension, renal artery stenosis, abnormal pulmonary arteries, and stenosis and rarefication of coronary arteries [21].

B. Indirect evidence for arteriopathy in MIDs

Indirect evidence for arteriopathy in MIDs comes from a number of reports, suggesting that arterial vasculopathy contributes to the pathogenesis of MIDs. The first indication for vasculopathy in MIDs comes from the finding in patients with stroke-like lesions that they not only present with hyperintensity on diffusion-weighted images and apparent diffusion coefficient (ADC) maps but also as hyperintensity on diffusion weighted images and as hypointensity on ADC maps, indicative of cytotoxic edema [12]. Since the pathogenesis of stroke-like lesions is still unsolved, it remains possible that at least parts of the lesion are caused by ischemia. This assumption is supported by findings, which clearly indicate that MIDs not only present with stroke-like lesions but also with ischemic stroke [22]. Further indirect evidence for vasculopathy in MIDs derives from the findings that cerebral perfusion (blood flow) is decreased in patients with MELAS syndrome [1,23]. In a single photon emission computed tomography (SPECT) study on three MELAS patients carrying the m.3243A>G mutation and born to mothers with chronic progressive external ophthalmoplegia (CPEO), brain SPECT showed multiple areas of asymmetrically decreased perfusion, particularly in the posterior and temporal brain regions [23]. There was also crossed-cerebellar diaschisis. In a study on MELAS patients with stroke-like lesions, cerebral blood flow and blood volume were decreased in areas of a stroke-like lesion on perfusion CT studies [1]. Particularly, mean transit time and time to peak were prolonged within lesional and non-lesional areas [1]. Muscle biopsy in these patients showed large granular deposits in vessel walls on SDH-staining (SSV). Electron microscopy of blood vessels showed strikingly increased number of mitochondria and cristae swelling in endothelial and smooth muscle cells [1]. A further indirect indicator for arteriopathy in MIDs is the frequent association of MIDs with migraine or migraine-like headache [11]. The vascular nature of migraine is a non-disputed fact, although the exact mechanisms resulting in the clinical manifestations are still unsolved [24,25]. Another indirect indication for arteriopathy in MIDs comes from patients with CADASIL, which is due to mutations in the Notch3 gene. Clinical manifestations in these patients derive from cerebral microangiopathy and CADASIL patients frequently present with mtDNA mutations [26]. Investigations of CADASIL patients revealed that some of them developed clinical features of myopathy, that muscle biopsy shows morphological features of MIDs, that complex I activity may be reduced in some patients, and that some patients may accumulate mtDNA mutations [26]. Further indirect indications for vasculopathy include the finding of impaired CO2
reactivity of intracerebral arteries in patients with MIDs [27]. In a study on 13 MELAS patients transcranial Doppler (TCD) investigations under conditions of normocapnia, hypercapnia and hypocapnia showed decreased CO₂ reactivity of the median cerebral arteries in most of them [27]. In patients with MID it was also found that flow-mediated vasodilation is reduced compared to controls [28]. Reduced flow-mediated vasodilation was attributed to altered nitric-oxide generation and bioactivity and confirmed by enhanced 3-nitrotyrosine staining in small vessels of muscle tissue [28]. It was concluded that the vessel wall is a target of increased oxidative nitric stress in patients with MID [28]. A further argument for endothelial dysfunction in MID is the improvement of endothelial dysfunction upon treatment with oral L-arginin, a nitric oxide precursor [29].

IV. CONCLUSION

Based on a large number of direct and indirect evidence for vasculopathy in patients with MIDs it can no longer be neglected that smooth muscle cells or endothelial cells of large or small arteries may be affected by a mitochondrial defect. Arteriopathy in MIDs contributes significantly to the course and outcome in these patients and is often a cause of premature morbidity or mortality. Isolated vasculopathy in the absence of classical risk factors or typical manifestations of multisystem MID may represent the sole manifestation of a MID.

REFERENCES