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Mitochondrial vasculopathy

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Abstract

Mitochondrial disorders (MIDs) are usually multisystem disorders (mitochondrial multiorgan disorder syndrome) either on from onset or starting at a point during the disease course. Most frequently affected tissues are those with a high oxygen demand such as the central nervous system, the muscle, endocrine glands, or the myocardium. Recently, it has been shown that rarely also the arteries may be affected (mitochondrial arteriopathy). This review focuses on the type, diagnosis, and treatment of mitochondrial vasculopathy in MID patients. A literature search using appropriate search terms was carried out. Mitochondrial vasculopathy manifests as either microangiopathy or macroangiopathy. Clinical manifestations of mitochondrial microangiopathy include leukoencephalopathy, migraine-like headache, stroke-like episodes, or peripheral retinopathy. Mitochondrial macroangiopathy manifests as atherosclerosis, ectasia of arteries, aneurysm formation, dissection, or spontaneous rupture of arteries. The diagnosis relies on the documentation and confirmation of the mitochondrial metabolic defect or the genetic cause after exclusion of non-MID causes. Treatment is not at variance compared to treatment of vasculopathy due to non-MID causes. Mitochondrial vasculopathy exists and manifests as micro- or macroangiopathy. Diagnosing mitochondrial vasculopathy is crucial since appropriate treatment may prevent from severe complications.

Key words: Mitochondrial disorder; Multisystem; MtDNA; Phenotype; Vasculopathy; Arteriopathy; Angiopathy; Genotype

Core tip: Recently, it has been shown that rarely also the arteries may be affected in mitochondrial disorders, known as mitochondrial vasculopathy. Mitochondrial vasculopathy manifests as either microangiopathy or macroangiopathy. Clinical manifestations of mitochondrial microangiopathy include leukoencephalopathy, migraine-like headache, stroke-like episodes, or peripheral retinopathy. Mitochondrial macroangiopathy manifests as atherosclerosis, ectasia of arteries, aneurysm formation, dissection, or spontaneous rupture of arteries. The diagnosis relies on the documentation and confirmation of the mitochondrial metabolic defect or the genetic cause after exclusion of non-mitochondrial causes. Treatment is not at variance compared to treatment of vasculopathy

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INTRODUCTION

It is well established that syndromic and non-syndromic mitochondrial disorders (MIDs) manifest as mitochondrial multiorgan disorder syndrome (MIMODS) in the majority of the cases, either since onset of the disease or starting later during the disease course[1,2]. Organs or tissues involved in MIMODS are numerous but some are more frequently affected than others and some are better recognised as sites of involvement than others. Among the frequently affected organs are the muscle, brain, eyes, ears, endocrine organs, and the heart. Less frequently involved are the liver, pancreas, intestines, kidneys, blood, and skin. Hardly known and appreciated as possibly affected organs in MIDs are the lung and the arteries. Here we summarise and discuss recent findings concerning the involvement of the arteries, arterioles, and capillaries in MIDs (mitochondrial vasculopathy). Mitochondrial vasculopathy may manifest in large arteries (macroangiopathy) or the small arteries (microangiopathy). Microangiopathy is defined as vasculopathy of the small arteries, arterioles, capillaries, or venules[3]. This review aims at summarising and discussing recent findings concerning mitochondrial vasculopathy.

SEARCH STRATEGY

Data for this review were identified by searches of MEDLINE, Current Contents, EMBASE, Web of Science, Web of Knowledge, LILACS, SCOPUS, and Google Scholar for references of relevant articles using the search terms "vasculopathy", "macroangiopathy", "microangiopathy", "aortic ectasia", "dissection", "rupture", "aneurysm", "megadolichobasilar artery", "migraine", "migraine-like headache", "microvascular", and "stroke-like episode" in combination with "mitochondrial", "mtDNA", "respiratory chain", "oxidative phosphorylation", and "cytopathy". Randomized (blinded or open label) clinical trials, longitudinal studies, case series, and case reports were considered. Abstracts and reports from meetings were not included. Only articles published in English, French, Spanish, or German between 1966 and 2015 were considered. Appropriate papers were studied and discussed for their suitability to be incorporated in this review. Fifty-nine papers were identified as suitable to be discussed in this review. According to these papers mitochondrial vasculopathy may be classified according to various criteria.

CLASSIFICATION OF MITOCHONDRIAL VASCULOPATHY

Mitochondrial vasculopathy may not only be classified as micro- or macro-angiopathy but also as primary or secondary. Primary mitochondrial vasculopathy is due to affection of cells constituting the vessels by the causative metabolic defect. Secondary mitochondrial vasculopathy is due to affection of vessels secondary to the development of diabetes, hyperlipidemia, or arterial hypertension due to affection of organs other than the arteries by the metabolic defect. Additionally, mitochondrial vasculopathy may go along with clinical manifestations or without and it may occur in a focal or generalised distribution. Mitochondrial macroangiopathy and microangiopathy present with various manifestations.

Microangiopathy

Microangiopathy manifests clinically or may remain subclinical. Clinical manifestations of mitochondrial microangiopathy include leukoencephalopathy, migraine-like headache, stroke-like episodes (SLEs), or peripheral retinopathy. Subclinical manifestations include morphological abnormalities in mitochondria of vascular smooth muscle cells (VSMCs), of pericytes, or of endothelial cells[4].

Leukoencephalopathy: Leukoencephalopathy is a frequent central nervous system (CNS) abnormality in syndromic as well as non-syndromic MIDs. It may be patchy or confluent. It is so far unknown if leukoencephalopathy is due to a vascular pathology or represents a primary metabolic defect of neurons or glial cells. Evidence for a vasculopathy comes from several observations. In a 13yo mitochondrial encephalomyopathy, lactic acidosis, and SLEs (MELAS) patient with leukoencephalopathy post-mortem studies revealed generalised cerebral microangiopathy[5]. In a post-mortem study of two other patients with MELAS-syndrome due to the mtDNA mutation m.3243A > G, of which one also presented with migraine, COX-negative VSMCs were most frequently found in the walls of leptomeningeal and cortical arteries over all cerebral regions[6].

Migraine-like headache: Migraine-like headache is a frequent manifestation of syndromic and non-syndromic MIDs. Best known is migraine-like headache as a manifestation of MELAS-syndrome[7] but has been also reported in adult Leigh-syndrome[8], Alpers-Huttenlocher disease[9], myoclonic epilepsy with ragged-red fibers (MERRF)-syndrome[10], mitochondrial recessive ataxia syndrome[11], chronic progressive external ophthalmoplegia (CPEO)[12], Leber's hereditary optic neuropathy (LHON)[13], cyclic vomiting syndrome[14], mitochondrial depletion syndrome[15], and non-syndromic MIDs due to POLG1 mutations[16]. Among patients

carrying the m.3243A > G mutation the prevalence of migraine was 58%[7]. In a study of two patients with MELAS-syndrome, of which on one also had migraine, COX-deficiency and heteroplasmy rates of the causative mutation were highest in cortical and leptomeningeal arteries[6]. Though the pathogenesis of migraine-like headache is poorly understood there are some studies indicating vasculopathy in these patients. Vascular pathology is characterised by episodic changes of the diameter of small cerebral arteries[17]. According to the vascular hypothesis of migraine it is assumed that initially there is vasoconstriction followed by vasodilation[17,18]. A further hypothesis suggests that activation of the calcitonin-related peptide gene is responsible for hyperperfusion and migraine[19]. Additional evidence for mitochondrial dysfunction in migraine derives from the finding that increased influx of calcium increases oxidative stress, that muscle biopsy of patients with migraine may show mitochondrial abnormalities, that mtDNA polymorphisms may be increased in migraine patients, and that riboflavin, coenzyme-Q, niacin, and carnitine, all agents used in the treatment of MIDs, exhibit a beneficial effect for migraine[20].

SLEs: SLEs are the hallmark of MELAS-syndrome but may occur in other syndromic or non-syndromic MIDs as well. They are clinically indistinguishable from ischemic strokes but may additionally manifest with seizures, headache, confusional state, or lactic acidosis[21]. The morphological correlate of a SLE is the stroke-like lesion, which is not confined to a vascular territory and most frequently located in the temporo-occipital region[22]. Concerning the MRI findings of stroke-like lesions, acute, subacute, and chronic alterations have to be differentiated. In the acute and subacute stage there may be cortical hyperintensity on diffusion weighted imaging (DWI) and hypointensity on apparent diffusion coefficient (ADC) maps (cytotoxic edema). The subcortical compound of a stroke-like lesion in this stage shows up as hyperintensity on DWI and hyperintensity on ADC in the cortical and subcortical compound (vasogenic edema)[23]. However, there are also studies showing hyperintensity on DWI and hyperintensity on ADC (vasogenic edema) in the subcortical and cortical grey matter. Fluid attenuated inversion recovery (FLAIR) sequences in the acute stage may show hyperintensity and MR angiography prominent dilatation of arteries and PWI consecutive hyperperfusion in the affected areas[24]. On the contrary, PWI studies in the acute stage in another study showed decreased cerebral blood flow as well as decreased cerebral blood volume[23,25]. Mean transit-time and time-to-peak are prolonged in lesional and non-lesional areas. The chronic stage of a stroke-like lesion may show up as hyperintensity on FLAIR sequences and as iso- or hyperintensity on ADC maps[22]. 99mTc-hexa-methyl-propyl-eneamine-oxime single-photon emission CT (HMPAO-SPECT) of a stroke-like-lesion in the chronic stage may show hyperperfusion or a mixture of hypo- and hyperperfusion[19,23,26].

Three main hypotheses have been raised to explain the phenomenon. First, SLEs result from mitochondrial vasculopathy caused by dysfunction of VSMCs of the small cerebral arteries leading to disruption of the blood brain barrier and consecutive vasogenic respectively cytotoxic edema and neuronal death[19,21,23]. Second, mitochondrial dysfunction may secondarily cause impaired cellular or mitochondrial metabolism resulting in decreased mitochondrial energy production causing neuronal damage or neuronal death[21]. Third, an initial seizure may cause oxidative stress resulting in secondary metabolic break-down. An argument for the seizure hypothesis is that SLEs are frequently associated with seizures and that appropriate antiepileptic treatment may be beneficial also for stroke-like-episodes[27].

Microangiopathy of retinal arteries: LHON is a syndromic MID with subacute onset visual impairment leading to permanent blindness. Two thirds of these patients present with microangiopathy of the retinal arteries, characterised by increased tortuosity and ectasias[28-31]. The same vascular abnormalities may be also found in non-manifesting carriers of the disease. However, the pathogenetic role of these vascular changes remains questionable since not all LHON patients develop retinal microangiopathy[28]. In rare cases, retinal microangiopathy may spontaneously regress[32].

Subclinical mitochondrial vasculopathy: Further evidence for microangiopathy in MIDs comes from a study of 3 patients with MERRF, CPEO, and migraine respectively, each carrying the m.3243A > G mutation[33]. 99mTc-HMPAO-SPECT in these three patients revealed asymmetric hypoperfusion in various cerebral regions with predominance in the temporo-occipital regions[33]. In another study of 13 MELAS patients reactivity of the median cerebral artery to hypo- or hyper-capnia was decreased on transcranial Doppler sonography and there was crossed diaschisis[34]. In a study of patients with Leigh-syndrome capillary shunting was documented by cerebral MRI[35]. In a recent study of 16 MID patients carrying the m.3243A > G mutation, the m.8344A > G mutation, or a POLG1 mutation respectively, multiple ischemic-like lesions were found in the cerebellar cortex bilaterally[36]. The findings were attributed to dysfunction of VSMCs and endothelial cells[36]. Dysfunction of endothelial cells and VSMCs was made responsible for a breakdown of the blood-brain-barrier, resulting in extravasation of plasma proteins and disruption of tight junctions of endothelial cells[36]. In a patient carrying the m.3243A > G mutation histological studies of the skin and muscle showed extra-cellular matrix mineralization in blood vessel walls[37]. There was also a correlation between SDH histochemical staining and the number of mitochondria on electron microscopy[37]. In a boy with non-syndromic MID neuropathological work-up of the brain revealed spongiform changes, swelling of endothelial cells, and increased number of mitochondria

with abnormal cristae formation in pericytes and VSMCs[4]. In a girl with MELAS-syndrome generalised microangiopathy with reduced COX-activity was found in the cerebrum, myocardium, and skeletal muscle[38]. In a histopathological study of MELAS patients COX-deficiency and heteroplasmy rates were highest in cortical and leptomeningeal arteries[6]. In case muscular arteries are subclinically affected histological studies may show SDH hyperreactivity, also known as strongly-succinate dehydrogenase-reactive vessels (SSV)[26]. SSV may occur in MELAS[39-42], CPEO[43], MERRF[44], and MERRF/MELAS overlap syndrome[45]. SSV are usually normal for COX[44] but in 5 MERRF patients SSV were COX-negative[44]. Ultrastructural investigations may show cristae swelling and increased number of mitochondria in VSMCs and endothelial cells[25]. In patients with non-syndromic MID muscle biopsy showed vasculopathy with swollen endothelial cells and swollen and dysmorphic mitochondria in VSMCs and pericytes[4]. Muscle biopsy of MID patients may also show reduced NO bioactivity particularly in endothelial cells and VSMCs of these patients[46]. When studying chronic intestinal pseudo-obstruction in MNGIE patients it turned out that mtDNA depletion due to tyrosine phosphorylase gene mutations was also present in VSMCs and endothelial cells of small arteries within the gastrointestinal walls[47].

Macroangiopathy

Premature atherosclerosis: There is increasing evidence that abnormal premature primary atherosclerosis can be a prominent feature of MIDs. Though not systematically investigated, an increasing number of patients with mitochondrial atherosclerosis is reported indicating that premature atherosclerosis particularly in patients without classical risk factors for atherosclerosis occurs. In a 54yo male with recurrent hyper-CKemia, Leriche-syndrome developed in the absence of classical risk factors for atherosclerosis and despite regular extensive physical exercise in form of frequent bicycling[48]. In a MID patient carrying the m.617G > A mutation, recurrent embolic strokes originating from an internal carotid artery stenosis in the absence of classical risk factors for atherosclerosis was reported[19]. It was concluded that mtDNA mutations might be implicated in the development of macroangiopathy in MID patients[19].

Ectasia of arteries: Ectasia of arteries in MIDs has been described for the aorta and the cerebral arteries. Aortic root ectasia: Aortic root ectasia in MID patients has been first described by Brunetti-Pierri *et al*[49] in 2011 in 10 patients with non-syndromic MIDs. These ten patients had an increased Z-score of the aortic root width, which is zero per definition in controls. One of these patients was a female and ten were males, aged 0.5 to 11.5 years[49]. A further case with non-syndromic MID and aortic root ectasia has been recently recognised. In a 84yo female with suspected non-syndromic MID, ectasia of the aortic root was diagnosed on X-ray of the lungs and confirmed by CT of the aorta. Most likely, aortic root ectasia is more frequent among MID patients than so far appreciated. However, except for the study by Brunetti-Pierri *et al*[49] no further systematic investigations regarding this issue have been conducted. It is unknown if aortic root ectasia in MIDs is associated with an increased risk of aortic dissection type A. It is also unknown if MID patients with aortic root ectasia have a worse prognosis compared to MID patients without. Ectasia of cerebral arteries: Ectasia of arteries in MIDs has not only been reported for the aorta but in a single patient also for the basilary artery[50]. In a 70yo female with suspected MID, ectasia of the basilary artery has been demonstrated[50]. Originally, the patient was admitted for an ischemic stroke in the posterior leg of the left internal capsule. Features suggesting MID in this patient included leukoencephalopathy, short stature, and hyperlipidemia[50]. Since megadolichobasilar arteries are not infrequent, these patients should undergo investigations for a MID if time of flight angiography on cerebral MRI or CT angiography show ectasia of the cerebral arteries. Additionally, patients with a MID should be investigated for ectatic cerebral arteries as a CNS manifestation of the disease. Pathogenetically, it can be suspected that there is impaired innervation of the arterioles and thus reduced tone of the vessel wall, that there is a decrease of collagen fibers, or impairment of the VSMCs due to metabolic dysfunction. It is also conceivable that arterial ectasia is congenital without progression during the further course.

Aneurysm formation: Cerebral aneurysms are the most frequent cause of subarachnoid bleeding with often poor or fatal outcome[51]. Particularly, in cases with hereditary subarachnoid bleeding with maternal trait of inheritance a MID should be suspected and affected patients investigated appropriately. Also in cases of accidental detection of a cerebral aneurysm, which is the most frequent mode how cerebral aneurysms are diagnosed, the family history is of great importance and in case there are indications for a MID in one of the family members, appropriate diagnostic work-up should be initiated also in other family members. Since cerebral aneurysms may occur in a familial distribution it appears justified not only to investigate MID patients for cerebral aneurysms but also their affected and non-affected relatives. A pseudoaneurysm of the right internal carotid artery was found in a 47yo female with MELAS-syndrome[52].

Dissection: Spontaneous dissection of the carotid artery is a rare manifestation of a MID and has been reported only in five patients thus far[37,52,53]. In a patient carrying the mtDNA mutation m.3243A > G spontaneous dissection of the internal carotid artery and of the vertebral arteries was reported[37]. Skin and muscle biopsy in this patient revealed ragged-red fibers (RRFs), regional variability of succinate-dehydrogenase (SDH) histochemical reactivity, morphologically abnormal mitochondria, and accumulations of mitochondria[37].

Similar mitochondrial abnormalities and extracellular matrix mineralisation were found in arterial walls[37]. In three further patients with suspected MID, spontaneous dissection of the carotid artery and the posterior cerebral artery have been described[53]. Muscle biopsy in these patients revealed RRFs, SDH hyporeactivity, and COX-negative fibers[53]. These abnormalities were made responsible for the development of arteriopathy with dissection. Possibly, more MID patients have experienced arterial dissection but were either not reported or a causal relation was not assumed. Neurosurgeons, vascular surgeons, and neurologists must be aware of MIDs as the cause of carotid artery dissection and each patient with carotid artery dissection but without an evident cause should be investigated for a MID as well. Treatment is not at variance from that of dissection due to non-mitochondrial causes. The fifth patients is a 47yo female with mitochondrial myopathy due to the m.3243A > G mutation who presented a right carotid artery dissection with consecutive ischemic stroke in the right median cerebral artery territory[52].

Spontaneous rupture of arteries: In a 15yo girl with MELAS-syndrome due to the m.3243A > G mutation spontaneous rupture of the aorta during insertion of a gastrostomy has been reported[54]. Rupture of the aorta was attributed to affection of the aortic wall by the metabolic defect since post-mortem histological examination had revealed disorganised layers of VSMCs, disrupted elastic layers, and decreased COX staining of VSMCs of the vasa vasorum of the aorta[54]. Additionally, PCR and RFLP revealed a mutation load of 40% in blood lymphocytes but 85% in arteries[54]. Interestingly, the family history was positive for arteriopathy since the mother of this girl had died from rupture of a major artery during angiography[54]. Unfortunately, it was not mentioned if the deceased mother also suffered from a MID or not and if she manifested in organs other than the arteries[54].

Vascular malformations: In a single patient with LHON due to the mtDNA mutation m.11778G > A in the *ND4* gene, conventional cerebral angiography after right thalamic bleeding at age 9yo revealed an arteriovenous malformation with feeders from the posterior thalamo-perforat artery[55].

Reduced flow-mediated vasodilation: Flow-mediated vasodilation (FMD) is defined as change in diameter of an artery as assessed by high-resolution ultrasound in response to the release of an inflated cuff proximal to the measurement[26]. In a study of 35 patients with MELAS-syndrome the FMD was generally reduced[26]. In a study of 12 patients with a MID the FMD was reduced compared to controls[56].

DIAGNOSIS

Diagnosing mitochondrial vasculopathy is not at variance from non-mitochondrial vasculopathy. The diagnosis relies on the documentation and confirmation of the mitochondrial metabolic defect or the genetic cause and the exclusion of non-MID causes. In case of SLEs it is advisable to additionally carry out EEG recordings.

TREATMENT

Treatment of mitochondrial vasculopathy is not at variance from treatment of non-mitochondrial vasculopathy but patients with SLE may profit from L-arginine, vitamins, and coenzyme-Q[57]. Administration of co-factors may be also beneficial for MID patients with migraine-like headache. L-arginine may improve the FMD on a long-term basis[26].

DISCUSSION AND CONCLUSION

Diagnosing mitochondrial vasculopathy is important since it has several clinical implications. First, recognition of vasculopathy of undetermined cause may lead to the diagnosis of a MID. Diagnosing MIDs is important since many MIDs are frequently non-recognised for years or under-diagnosed. Mitochondrial vasculopathy most obviously indicating a MID as the underlying pathology is a stroke-like lesion. This is evident since stroke-like lesions are hallmarks of some MIDs and do not occur in disorders other than MIDs. Mitochondrial vasculopathy second most frequently indicative of a MID as an underlying cause is migraine[7]. Migraine is a frequent phenotypic feature of several syndromic and non-syndromic MIDs[7]. It may present not always as classical migraine why it is often termed migraine-like headache. Recent studies have shown that certain mtDNA polymorphisms are increased in patients with migraine[58]. There is also a mild bias towards a maternal transmission of migraine[59]. This is why patients with migraine should be suspected to have a MID as the underlying cause, as long as other possible causes have not been definitively excluded. Second, mitochondrial vasculopathy should be included as a phenotypic manifestation of syndromic or non-syndromic MIDs. Diagnosing MIDs should urge those manging MID patients to look for mitochondrial vasculopathy in individual patients and to initiate measures of treatment and prevention. Third, patients with MIDs should be systematically investigated for mitochondrial vasculopathy. This is important since MID patients are not investigated for concomitant mitochondrial vascular disease unless it is the dominant feature or leads to the diagnosis of LHON. Systematic investigations of MID patients for mitochondrial vasculopathy are important since early diagnosis may prevent severe complications. Systematic search for mitochondrial vasculopathy may contribute to assessing the prevalence of mitochondrial vasculopathy.

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