Case Report

Mitochondrial m.3243A→G mutation and carotid artery dissection

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A B S T R A C T

The common m.3243A→G mutation of the mitochondrial DNA tRNALeu (UUR) gene is a maternally inherited mutation causing a wide spectrum of neurological and multisystemic disorders, including MELAS, characterized by recurrent cerebral infarction from young age. Vascular pathology in mitochondrial diseases has been described for small vessels, while large vessels involvement in mitochondrial diseases is considered rare. Here we report two female patients harboring the m.3243A→G mutation, in whom the diagnosis of mitochondrial disease was made after acute dissection of the internal carotid arteries. Our cases expand the clinical spectrum of this mutation, and support the idea of large vessels vasculopathy due to impaired mitochondrial function in the vessel wall that may lead to arterial wall weakness. Thus, stroke in mitochondrial diseases could also be related to large vessels disease, but further studies are strongly needed. Moreover, mitochondrial aetiology should be kept in mind in patients with large vessel dissection, especially in those with additional mitochondrial red flags.

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1. Introduction

The m.3243A→G mutation is one of the most common point mutation of the mitochondrial genome (mtDNA). Several clinical syndromes have been ascribed to this mutation, including mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS), maternally inherited deafness and diabetes and progressive external ophthalmoplegia, but heterogeneity is high [1]. Other features include pure myopathy, cardiomyopathy, seizures, migraine, ataxia, cognitive impairment, gastro-intestinal dysmotility and short stature [1].

So far, there is a large amount of data supporting the involvement of small vessels in mitochondrial disease and their dysfunction in stroke-like episodes. The “mitochondrial angiopathy” is characterized by accumulation of mitochondria within vascular endothelial cells and smooth muscle cells in cortical, white matter and leptomeningeal small arteries and arterioles [2]. Only a few case on large vessels involvement in mitochondrial diseases are well documented.

Here we report two patients harbouring the m.3243A→G mutation in whom the diagnosis was performed after acute internal carotid artery dissection.

2. Patients and methods

2.1. Case 1

A 37-year-old Italian woman was admitted because of neck pain and intense headache associated with right eyelid ptosis and ipsilateral ministroke. Her past medical history revealed a progressive sensor neural hearing loss and migraine without aura from infancy, diabetes mellitus and macular retinopathy from age 36. She also complains of mild myalgias and exercise intolerance. No history of recent major head trauma or cervical manipulation was revealed. Her family history was unremarkable also for known blood vessel abnormalities.

Routine laboratory exams revealed mild increment of basal lactate (24 mg/dL; normal ~ 21) and glycaemia (136 mg/dL, range 50–110). The remaining exams, including thrombophilic and rheumatologic screening, were negative. The MR angiography (MRA) of brain and neck vessels demonstrated occlusion of pre- and intra-petrosal right internal carotid artery (Fig. 1). Brain MRI was normal as well as proton spectroscopy. Echocardiography was normal, as well as other detectable body vessels.

Molecular analysis of TGFR1, TGFR2 and COL3A1 genes were normal. Because of the mild hyperlactacidemia and the presence of mitochondrial “red flags” such as diabetes mellitus, hearing loss and maculopathy, a quadriceps muscle biopsy was performed, and numerous ragged red/ragged blue fibers and COX-negative fibers were detected. MtDNA analysis revealed the A → G transition at position 3243 of the...
mtDNA encoded MT-TL1 gene, detected in 60% and 70% of mtDNA form muscle and urinary sediment respectively. At one year follow up, MRA showed partial recanalization of the right internal carotid and no evidence of pseudoaneurysmal dilatation.

2.2. Case 2

An Italian 50 years-old woman developed sudden speech disturbances and mild right arm strength reduction, followed by epileptic seizures. There was no history of recent major head trauma or cervical manipulation. Her past medical history revealed a progressive deafness since her 30s, which was also present in her mother (who died at 74-ys because of stroke), her son and in a maternal aunt. She also suffered from migraine attacks since young age. No known blood vessel abnormalities are known in the pedigree.

A brain CT scan showed a left temporal-parietal cortical stroke-area, confirmed by a brain MRI, and basal ganglia bilateral calcifications. The arteriography showed a bilateral carotid dissection in the petrous segment (Fig. 2); the left artery dissection brought to a stenosis and a pseudoaneurismatic lesion, while the right one was completely collapsed. No other body vessels were involved.

Blood tests, including basal lactate, rheumatological and thrombophilic screening, were normal, as well as the genetic screening for collagen syndromes (COL1A1, COL1A2, COL3A1, COL5A1, COL5A2). The common mutation m.3243A>G was present in 30% of mtDNA from urinary sediment, and absent on blood’s leukocytes. Muscle biopsy was not performed.

3. Discussion

Our report describes two females in whom the diagnosis of mitochondrial disease was made after acute carotid artery dissection leading to a neurological syndrome. Our findings further broaden the clinical spectrum of the m.3243A>G mutation, document a possible role of mitochondrial involvement in large vessels dissection, and suggest a mitochondrial screening in patients with carotid artery dissection, at least when canonical mitochondrial red flags are present [1].

Vascular pathology in m.3243A>G MELAS has been extensively described for small vessels. Histological examination of muscle biopsy shows the so-called strongly SDH reactive blood vessels, indicating mitochondrial proliferation. The pathogenesis of stroke-like episodes in MELAS is not fully understood although two main theories have been proposed: the “ischemic vascular” hypothesis caused by a mitochondrial angiopathy and the “metabolic and neuronal hyperexcitability” hypotheses [3]. A neuropathological study [2] showed vascular abnormalities, characterized by proliferation of enlarged mitochondria in smooth muscle cells and endothelium of small cortico-leptomeningeal vessels. The same study also showed the highest m.3243A>G mutation load in the vessels wall (99%) and severe cytochrome c oxidase (COX) deficiency, arguing that the mitochondrial pathology of small vessels leads to an altered vascular tone and that vascular abnormalities are the primary cause of ischemia and stroke-like episodes.

The first report of large-vessels involvement in MELAS came from Dr. Di Mauro’s Lab [4], a 15-year old girl who died after minor surgical procedure of spontaneous rupture of thoracic aorta; her mother also died of ruptured vessels. The authors observed severe mitochondrial
dysfunction in the vessel wall leading to disruption of the smooth muscle layers directly or through impaired blood supply due to vasa vasorum angiopathy. Immunohistochemical staining for COX showed decreased COX I staining in smooth muscle cells and endothelial cells of vasa vasorum. The m.3243A→G mutation load in the ruptured aortic wall was 85% compared with 40% in blood.

Nemes and coworkers [5] studied ascending aorta elasticity through transthoracic echocardiography in m.3243A→G patients, and found an increased aortic stiffness, enlarged aortic dimension and reduced aortic strain and distensibility, suggesting vascular remodelling and alteration in aortic elasticity.

Another report suggested that in some cases stroke-like episode could subdue a large vessel dysfunction: during the acute phase of the first stroke-like episodes in a 26-year old woman with MELAS, a transient narrowing of the crural segment of posterior cerebral artery was observed [6]. Similarly, a case of MELAS who presented with transient narrowing of the crural segment of posterior cerebral artery involving cerebral arteries junction resolved after intravenous L-arginine supports the role of nitric oxide as a key factor in the pathogenesis of stroke-like episodes and vasospasm [7]. Moreover, transient and recurrent stenosis or occlusion of both carotid arteries with spontaneous resolution associated with stroke has been described in a case of mitochondrial encephalomyopathy due to a tRNAPh mtDNA mutation [8]. The authors suggested degenerative changes or a developmental abnormality as main cause of the stenosis, because the carotids appeared smooth, thin and without calcification to vascular imaging and no signs of dissection of the wall were present [8]. Finally, vascular stenosis may be rarely progressive in the setting of mitochondrial disease; Longo and collaborators described the case of a child harboring a m.3243A→T mutation with a rapidly evolving brain involvement due to progressive stenosis of both distal carotid and origin of cerebral arteries with development of collateral circulation, resembling a Moya Moya syndrome [9].

So far, although there is a growing list of monogenic disorders associated with cervical artery dissection [10–11], only one case of dissection of the cervical arteries associated with the m.3243A→G has been described, a case of a 47-year old woman who underwent recurrent dissection of internal carotid artery during stroke-like episodes [12], as observed in our Case 2.

Our report provides further evidence about a large vessels involvement in mitochondrial diseases. In some cases, mitochondrial dysfunction in endothelium and in smooth muscle cells may cause energy failure of the carotid wall, thus predisposing to vessel pathology like dissection, vasospasm, rupture or ischemia contributing, by means of hypoperfusion and artery-to-artery embolism, to the overall stroke burden in mitochondrial disease. Interestingly, both our patients suffered also of migraine which has been suggested as a risk factor for cervical artery dissection; migraine is also a common sign of m.3243A→G population [1], and vascular and mitochondrial dysfunctions have also been implicated in migraine [13].

Though we cannot provide histopathological demonstration of a mitochondrial dysfunction in the carotid artery, we can hypothesize that the dissection of the carotid artery as described in our cases could be seen as the tip of the iceberg of a more diffuse and subtle vascular mitochondrial dysfunction. Moreover, additional canonical risk factors leading to ischaemic stroke or dissection were screened, and were negative in both cases. Diabetes, present in our Case 1, should not play a major role in the pathogenesis of the dissection, because it is well known from the CADISP studies that all traditional vascular risk factors, including diabetes, are less frequent in cerebral artery dissection patients compared with young patients with a non-cervical artery dissection ischaemic stroke [14].

Further studies are needed to evaluate the association between mitochondrial disease and large vessels pathology.

Conflict of interest

None.

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