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COMMENTARY

Macroangiopathy is a typical phenotypic manifestation of MELAS

Josef Finsterer[1] · **Sinda Zarrouk-Mahjoub**[2]

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With interest we read the article by Zhu et al. about a 54yo male with MELAS due to the mutation m.3243A > G in the *tRNA*$^{(Leu)}$ gene manifesting as short stature, stroke-like episodes (SLEs), and macroangiopathy (Zhu et al. 2017). We have the following comments and concerns.

Macroangiopathy is a typical phenotypic feature of mitochondrial disorders (MIDs) but is even more frequently not attributed to the underlying metabolic defect (Finsterer and Zarrouk-Mahjoub 2016). Macroangiopathy in MIDs may manifest as atherosclerosis, ectasia of arteries (aortic root, intracerebral arteries, abdominal aorta) (Finsterer and Zarrouk-Mahjoub 2016), aneurysm formation (intracerebral arteries) (Zhu et al. 2017), as arterio-venous malformation (Scuderi et al. 2015), or as reversible vasoconstriction (Yoshida et al. 2013) (Table 1). The reason why macroangiopathy is not more frequently attributed to a MID is due to the fact the MIDs go frequently undetected for years and is often misdiagnosed and mistreated. Particularly in case of atherosclerosis but absence of classical risk factors or frequent sport activity a mitochondrial defect must be considered.

Macroangiopathy in MIDs may be complicated by dissection (internal carotid artery) or spontaneous rupture (aorta) (Table 1). Spontaneous rupture of intracerebral arteries may cause intracerebral bleeding (Fujitake et al. 2002) or sudden death in case of aortic rupture. An argument in favour of a MID manifesting as cerebral aneurysm is that in patients with subarachnoid bleeding intracerebral microdialysis was indicative of mitochondrial dysfunction in 29/55 patients with subarachnoid bleeding (Jacobsen et al. 2014).

mtDNA mutations are usually maternally inherited and only rarely occur spontaneously. Was the family history positive for MELAS, in particular, did the mother present with any features typical for MELAS? Did the mother or other first degree relatives carry the same mutation as the proband? Were other family members investigated for cerebral aneurysms? Was the family history positive for subarachnoid bleeding?

Severity of clinical manifestations may depend on the amount of mutation present within a tissue. Was the heteroplasmy rate determined and was there a difference between tissues such as hair follicles, buccal cells, fibroblasts, muscle cells, urine bladder epithelial cells, or lymphocytes? Was the heteroplasmy rate determined from a biopsy of an artery?

The patient was obviously admitted because of a SLE, manifesting as epilepsy, visual impairment, and headache (Zhu et al. 2017). Which type of headache did the patient present with? Was it migraine or migraine-like headache? What type of therapy did he receive for cephalalgia? NO-precursors have been shown beneficial for SLEs. Did the patient receive L-arginine or L-citrulline in addition to coenzyme-Q and levetiracetam? Was the patient put on a ketogenic diet, which has been shown to be beneficial particular for mitochondrial epilepsy and migraine-like headache?

Josef Finsterer and Sinda Zarrouk-Mahjoub contributed equally to this work

✉ Josef Finsterer
fifigs1@yahoo.de

[1] Krankenanstalt Rudolfstiftung, Postfach 20, Vienna, Austria

[2] Pasteur Institute of Tunis, University of Tunis El Manar and Genomics Platform, Tunis, Tunisia

Table 1 Macroangiopathy in MIDs

Type of macorangiopathy	Location	Mutation	Mt syndrome	Reference
Atherosclerosis	Aorta/iliac	nm	nsMIMODS	(Finsterer and Stöllberger 2015)
	ICA	m.617G > A	nsMIMODS	(Iizuka et al. 2009)
Ectasia	Aortic root	nm	nsMIMODS	(Brunetti-Pierri et al. 2011)
	Aortic root	nm	nsMIMODS	(Finsterer, submitted)
	BA	nm	nsMIMODS	(Finsterer and Bastovansky 2015)
Aneurysm formation	ICA	m.3243A > G	MELAS	(Zhu et al. 2017)
	ICA	m.3243A > G	MELAS	(Ryther et al. 2011)
Arteriovenous malformation	PCC	m.11778G > A	LHON	(Fujitake et al. 2002)
	Cerebral	POLG1	nsMIMODS	(Scuderi et al. 2015)
Revesible vasoconstriction	ICA + MCA	m.3243A > G	MELAS	(Yoshida et al. 2013)
	PCA	nm	MELAS	(Noguchi et al. 2005)
Dissection	ICA	m.3243A > G	MELAS	(Ryther et al. 2011)
	ICA	m.3243A > G	MELAS	(Sakharova et al. 2012)
	ICA + VA	nm	nsMIMODS	(Kalashnikova et al. 2012)
	ICA	m.3243A > G	nsMIMODS	(Mancuso et al. 2016)
Rupture	Aorta	m.3243A > G	MELAS	(Tay et al. 2006)

ICA Internal carotid artery, *MCA* Median cerebral artery, *PCA* Posterior cerebral artery, *Nm* Not mentioned, *nsMIMODS* non-specific mitochondrial multiorgan disorder syndrome, *BA* Basilary artery, *PCC* Posterior cerebral circulation, *VA* Vertebral artery

Since cerebral aneurysms may increase in diameter over time we should be informed if follow-up investigations were carried out and if there were dynamic changes of the aneurysm over time.

Overall, the report would profit from an extensive family history and genetic investigations of first degree relatives. Macroangiopathy is not restricted to MELAS but has to be regarded as a phenotypic manifestation in other MIDs as well. Patients with subarachnoid bleeding should be investigated for MID.

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Compliance with ethical standards

Conflict of interests There are no conflicts of interest.

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