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Letter to Editor

Phenotype of mitochondrial *cytb* mutations

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Letter to the Editor

In a recent article, Mancuso et al. reported about a 19 years-old girl with MELAS syndrome due to the *cytb* mutation m.15092G>A [1]. We have the following comments and concerns.

Mutations in the mitochondrial *cytb* gene may not only present as MELAS syndrome but with a large phenotypic variability (table 1). Either a single organ may be affected or several organs are involved (table 1).

Table1. Phenotypic manifestations of mitochondrial *cytb* mutations

Reference	Patient	*cytb* Mutation	Phenotype
Mancuso 2014	19y/f	m.15092G>A	MELAS (SLE, focal epilepsy)
Emmanuele 2013	15y/f	m.14864T>C	Migraine, neuropathy, SLE
Sobenin 2013	na	m.15059G>A	Essential hypertension
Zarrouk-Mahjoub 2012	na	m.15434C>A	Dilated cardiomyopathy
Gutierrez-Cortez 2012	na	m.15077G>A	Hearing loss
Sundaram 2011	na	na	CPEO
Ronchi 2011	15m/f	m.14459G>A	Leigh syndrome
Zaragoza 2011	na	m.15132T>C	Hypertrophic and dilated cardiomyopathy
Gil Borlado 2010	23d/m	m.15533A>G	Epilepsy, cognitive impairment
Kato 2010	na	m.15498G>A	Hearing loss
Massie 2010	18y/m	m.14849T>C	Myopathy, exercise intolerance
Houshmand 2004	57y/f	mtDNA duplication	Depression, hypoacusis, diabetes, EMP
Finsterer 2000	33y/m	m.15812G>A	MODS
Marin-Garcia 2000	5m/m	m.15236	Hypertrophic cardiomyopathy
Marin-Garcia 2000	6m/f	m.15508	Dilated cardiomyopathy
Keightley 2000	34y/f	m15242G>A	Exercise intolerance, lactic acidosis
De Coo 1999	young boy	4bp-deletion	SLE
Marin-Garcia 1996	na	m.15452C>A	ischemic cardiomyopathy
Nigro 1990	18y//f	na	torsion dystonia, myopathy

Yo: years-old, f: female, m: male, ns: not available, SLE: stroke-like episode, CPEO: chronic progressive external ophthalmoplegia, MODS: multi-organ disorder syndrome, EMP: encephalomyopathy

The mutation is said to affect the stability of complex III. Were any animal model studies carried out to confirm the pathogenicity of the mutation? A similar effect in the animal model would confirm the pathogenicity of the mutation.

There is no need in MELAS patients to perform cerebral biopsy. Which was the indication for this invasive measure? The authors themselves mention that the tissues best suitable for genetic testing of mitochondrial disorders are the muscle and the urinary sediment. Only if there are indications for a second trouble, cerebral biopsy may be of diagnostic support. If at all cerebral biopsy was done, molecular studies should have been carried out to confirm the *cytb* mutation in the brain tissue.

Stroke-like lesions (SLLs) are usually not space-occupying. Is it possible that the mass effect reported was due to an ischemic stroke or focal cerebral edema from focal seizures? Were hyperintense lesions on diffusion weighted images and hypointense lesions on corresponding ADC maps observed? Is it conceivable that the SLLs actually represent an epileptic epiphenomenon? Was there focal paroxysmal EEG activity in the areas of the SLLs?

It is unusual to perform craniotomy for a SLL. For how many millimetres was the midline shifted? Were other measures, such as anti-edema therapy, applied to reduce the mass effect of SLLs? Did the mass effect occur only with one or with each SLL?

In recent studies it has been shown that L-arginine is effective to reduce duration and intensity of SLLs [2,3]. Did the patient receive L-arginine or other non-specific drugs to recover from recurrent, multifocal SLLs?

Why was phenytoin applied as an antiepileptic drug? It is well-known that phenytoin reduces state-3-respiration, the mitochondrial membrane potential, and ATP-production, increases state-4-respiration, impairs calcium uptake and release, and inhibits calcium-induced swelling, mitochondrial Na/K-ATPase, and the Mg-ATPase [4].

There is definitively cardiac involvement in MELAS [5]. Thus, one echocardiography is not enough to rule out cardiac disease. Did the patient undergo long-term ECG-recording (Holter, telemetry, reveal)? Which were the results of long-term ECG recordings? Was the individual or family history positive for syncope, fainting, or (near) sudden cardiac death (SCD)? Were ever supra-ventricular or ventricular arrhythmias, in particular atrial fibrillation or ventricular runs, recorded? Did she ever present with supra-ventricular or ventricular conduction delay?

How do the authors explain the discrepancy between MRS showing high lactate and CSF investigations showing normal CSF lactate?

Overall, this interesting case shows that extensive work-up for MELAS is not always necessary. Cerebral biopsy is not indicated in MELAS patients unless a second trouble is suspected. Mitochondrion-toxic medication should be avoided in MELAS patients. The phenotypic variability of *cytb* mutations is high.

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