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Letter to Editor

Genetic background and phenotypic heterogeneity of MELAS and maternally inherited diabetes and deafness

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Letter to the editor

With interest we read the article by Li et al. about a family with mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) syndrome [1]. We have the following comments and concerns.

The m.3243A>G mtDNA mutation may not only cause MELAS and maternally inherited deafness and diabetes (MIDD) but also MELAS/myoclonic epilepsy and ragged red fibers (MERRF) overlap syndrome, chronic progressive external ophthalmoplegia (CPEO), Kearns-Sayre syndrome (KSS), Leigh syndrome, floppy infant syndrome, non-syndromic entero-myopathy, or other non-syndromic mitochondrial disorders (MIDs) [2].

MIDD is not only characterised by insulin-deficient diabetes and hearing loss but may also include epilepsy, cerebellar ataxia, renal insufficiency not related to the diabetes, focal segmental glomerulosclerosis, hyporeninemic hypoaldosteronism, maculopathy, retinopathy, cognitive impairment, cataract, hypothyroidism, renal insufficiency, stroke, intestinal pseudoobstruction, WPW-syndrome, myopathy, basal ganglia calcification, dilated cardiomyopathy, short stature, pancreatitis, hypoparathyroidism, Parkinson syndrome, Addison disease, and cerebral atrophy (**Table 1**).

Though MIDD is due to the m.3243A>G mtDNA mutation in 85% of the cases [3], it may be also due to the m.9276G>C mutation in the COXIII gene, the m.1555A>G in the 12S rRNA gene, the m.3308T>C mutation in the ND1 gene, the insertion m.14535_14536C or CC, the m.14709T>G mutation, the m.3421G>A mutation, the m14709T>C mutation, the 8381 mtDNA mutation, or due to a mtDNA deletion (**Table 1**).

The index case is reported as having headache in addition to seizures, nausea, and vomiting [1]. Which type of headache did the authors diagnose? Did the patient report a history of migraine or cluster headache, headache types occasionally associated with MID [4, 5]. Was nausea and vomiting independent of headache or always associated with it?

It is reported that MELAS in the presented patient manifested with epilepsy [1]. Which type of seizures did the patient develop, which was the frequency of seizures, which type of antiepileptic treatment did the patient receive, and how effective was the seizure control? Since seizures can be associated with stroke-like episodes and respond to L-arginine, it would be interesting to know if seizures in the described patient were associated with stroke-like episodes each time and if she received L-arginine? Did the patient ever experience an epileptic state?

It would be also interesting to learn more about the treatment and course of diabetes. Which were the HbA1c values? Which secondary complications of diabetes did the patient develop?

Table 1. Clinical manifestations other than diabetes and deafness and mutations other than the m.3243A>G in MIDD

NOP	Sex	Age	ACM	Mutated gene	Reference	FP/AB
Other manifestations						
3	3 f	nm	Nephropathy	m.9276G>C, COXIII	[Tabebi 2015]	AB
1	f, nm	65	Convulsion, cerebellar ataxia	m.3243A>G	[Imamura 2015]	FP
2	nm	nm	MELAS	m.3243A>G	[Lauterlein 2014]	AB
1	f	46	Maculopathy, migraine	m.3243A>G	[Daruich 2014]	FP
2	2 f	39/14	Focal glomerulosclerosis	m.3243A>G	[Cao 2013]	FP
1	f	70	Outer retinal tabulations	m.3243A>G	[Raja 2013]	FP
1	m	50	Hyporeninemic hypoaldosteronism	m.3243A>G	[Mory 2013]	FP
1	m	33	MELAS	m.3243A>G	[deWit 2012]	FP
1	f	67	CMP, cognitive impairment	m.3243A>G	[Kato 2012]	FP
1	f	54	Ptosis	m.3243A>G	[Ogun 2012]	FP
1	m	68	Hypothyroidism, maculopathy, cataract	m.3243A>G	[Strauss 2012]	FP
1	f	52	CMP, cognitive impairment	m.3243A>G	[Gerber 2011]	FP
1	m	59	CMP, renal insufficiency	m.3243A>G	[Azevedo 2011]	FP
11	5 m, 6 f	53.6	Cognitive decline, ataxia, CMP, stroke	m.3243A>G, 14709T>G	[Fromont 2009]	FP
1	f	47	Intenstinal pseudoobstruction	m.3243A>G	[Bergamin 2008]	FP
1	f	44	WPW-syndrome, myopathy	m.3243A>G	[Donovan 2006]	FP
2	f, m	67, 41	Cerebral atrophy	m.3243A>G	[Kobayashi 2005]	FP
1	f	48	Basal ganglia calcification, stroke, SS	m.3243A>G	[Chen 2004]	FP
10	nm	nm	Gastrointestoinal pseudoobstruction	m, 3243A>G, 14709T>C	[Narbonne 2004]	AB
1	m	54	Dilated cardiomyopathy	m.3243A>G	[Silveiro 2003]	FP
13	5 m, 8 f	8-74	Cerebral atrophy, calcifications, SS	m.3243A>G	[Lien 2001]	FP
1	f	27	Pancreatitis, seizures	m.3243A>G	[Schleiffer 2000]	AB
1	f	54	Hypoparathyroidism	m.3243A>G	[Tanaka 2000]	FP
13	9 f, 4 m	23-86	Pigmentary retinal dystrophy	m.3243A>G	[Smith 1999]	FP
10	4 f, 6 m	4-63	Addison, Parkinson	m.3243A>G	[Thorns 1998]	FP
1	m	35	Cerebellar ataxia	m.3243A>G	[Arai 1997]	FP
Other mutations						
3	3f	nm	Nephropathy	m.9276G>C, COXIII	[Tabebi 2015]	AB
1	f	44	None	m.1555A>G, 12S rRNA m.3308T>C, ND1	[Mezghani 2013]	AB
1	m	77	None	m.14535_14536insC, CC	[Bannwarth 2011]	FP
11	5 m, 6 f	53.6	Cognitive decline, ataxia, CMP, stroke	m.3243A>G, 14709T>G	[Fromont 2009]	FP
5	nm	nm	None	5 new mutations	[Crispim 2008]	FP
14	9 m, 5 f	35-42	None	m.3421G>A	[Chen 2006]	FP
10	nm	nm	Gastroontestoinal pseudoobstruction	m.3243A>G, 14709T>C	[Narbonne 2004]	AB
1	nm	nm	None	m.14709T>C	[Peruccia 2002]	FP
1	nm	nm	None	m.8381	[Perruccia 2000]	AB
7	nm	45-53	Stroke	mtDNA del	[Ballinger 1992]	FP

NOP: number of patients, ACM: additional clinical manifestation, FP/AB: full paper, abstract, f: female, nm: not mentioned, CMP: cardiomyopathy, WPW: Wolff-Parkinson-White, SS: short stature.

Did the patient ever receive a biguanide and was ever lactacidosis diagnosed?

Overall, the didactic merit of this interesting case could be enhanced by providing and discussing essential lacking information. Patients with MIDD or MELAS are clinically and genetically more heterogeneous than anticipated.

Disclosure of conflict of interest

None.

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