East African Scholars Journal of Medical Sciences
Abbreviated Key Title: East African Scholars J Med Sci
ISSN 2617-4421 (Print) | ISSN 2617-7188 (Online) |
Published By East African Scholars Publisher, Kenya

OPEN ACCESS

Volume-2 | Issue-9| Sept -2019 | DOI: 10.36349/EASJMS.2019.v02i09.018

Letter to the Editor

Morphological Diversity of Stroke-Like Lesions May Depend On Heteroplasmy Rates and Haplotypes

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Keywords: mtDNA, deletion, multisystem, haplogroups, mitochondrial disorder, oxidative phosphorylation.

In a recent article, Saldana-Martinez *et al.*, reported about three patients with Kearns-Sayre syndrome (KSS) due to a single mtDNA deletion of 7629, 4977, and 5387 pb respectively (Saldaña-Martínez, A. *et al.*, 2019). Heteroplasmy rates of the variants were 84, 40 and 60% respectively (Saldaña-Martínez, A. *et al.*, 2019). We have the following comments and concerns.

We do not agree that all three patients had KSS. KSS is diagnosed upon clinical features if the three core features onset <20y of age, progressive external ophthalmoplegia (PEO), and pigmentary retinopathy, and at least one of the following features are present: CSF protein >100mg/dl, cardiac conduction defects, or cerebellar dysfunction (Finsterer, J. 2019)). In none of the three patients is pigmentary retinopathy reported (table 1). None of the three patients had ataxia or other indications for cerebellar dysfunction (table 1). Only one of the three patients had a conduction defect requiring a pacemaker. In none of the patients is reported if CSF protein was elevated or not (table 1). It is not reported if there was short stature, cognitive impairment or tremor. According to a literature review diabetes is not only present in some patients with KSS but in 14% percent of the cases (Finsterer, J., & Frank, M. 2015). At maximum an abortive KSS can be diagnosed but the full phenotype was present in none of the three patients.

Table 1. Clinical presentation of the three included patients

	Patient 1	Patient 2	Patient 3
General			
Age (y)	10	19	18
Sex	f	nm	m
Height	nm	nm	nm
Weight	nm	nm	nm
mtDNA deletion (bp)	7629	4977	5387
Heteroplasmy (%)	84	40	60
Cardinal features			
PEO	yes	yes	yes
Retinopathy	nm	nm	nm
CSF-protein ↑	nm	nm	nm
Additional features			
CCD	no	no	yes
Cerebellar inv.	no	no	no
Ataxia	no	no	no

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Journal homepage:
http://www.easpublisher.com/easjms/

Article History
Received: 24.08.2019
Accepted: 05.09.2019
Published: 19.09.2019

Other			
Hypoacusis	no	no	yes
Ptosis	yes	yes	yes
Muscle cramps	no	yes	no
Weight loss	no	no	yes
Cardiomyopathy	yes	yes	yes
Headache	no	no	yes
Visual acuity ↓	no	no	yes
Cognitive decline	nm	nm	nm
Exercise intolerance	no	no	yes

PEO: progressive external ophthalmoplegia, CSF: cerebrospinal fluid, inv. involvement, f: female, m: male, nm: not mentioned

We also do not agree that mtDNA re-arrangements affect only brain, nerves, muscle, heart or endocrine organs (Saldaña-Martínez, A. *et al.*, 2019). mtDNA re-arrangements affect each cell type of the body containing mitochondria with variable phenotypic expression. Thus, there is also frequent involvement of the eyes, ears, gastrointestinal tract, liver, kidneys, immune system, cartilage, and hematological system in patients with a mitochondrial disorder (MID) in general and particularly in KSS. Often the multisystem involvement is not obvious on routine testing why prospective investigations for subclinical involvement of any of the possibly affected tissues should be carried out.

We also do not agree with the statement that KSS is only due to mtDNA re-arrangements (Saldaña-Martínez, A. *et al.*, 2019). KSS has been reported also in association with variants in *SOX10* (Berio, A. *et al.*, 2017) or *RRM2B* (Pitceathly, R. D. *et al.*, 2011). Additionally, mtDNA point mutations such as in $tRNA^{(Leu)}$ have been reported in association with KSS (Yu, N. *et al.*, 2016; Kornblum, C. *et al.*, 2005; & Zhang, Y. *et al.*, 2005).

The authors mention that treatment of KSS "with some compounds" is available (Saldaña-Martínez, A. *et al.*, 2019). We should be informed which compounds they mean and how effective these therapies are. We should also know if they mean causative treatment or symptomatic treatment. This is of relevance as currently KSS is accessible only to symptomatic treatment. Compounds like CoQ, riboflavin, or L-carnitine are largely ineffective in MIDs. Prevention of the transmission of KSS in the 4% in which it follows a maternally trait of inheritance (Poulton, J. *et al.*, 2017), can be theoretically offered but has not been applied successfully so far.

Since patient 2 had muscle cramps we should be informed if the patient had undergone muscle biopsy and if mitochondrial myopathy was diagnosed. The term "cardiomyopathy" is not specified (Saldaña-Martínez, A. *et al.*, 2019). Thus, we should know if the authors mean hypertrophic, dilated, restrictive, histiocytoid, Takotsubo, or noncompaction cardiomyopathy.

Overall, this interesting case study could be more meaningful if the phenotype of the three included patients was more precisely described, if the three patients were prospectively investigated for multisystem disease, if point mutations were considered as causes of KSS, and if they were reclassified as MIDs not fulfilling all diagnostic criteria for KSS.

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