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Polyendocrinopathy and multisystem involvement are common phenotypic features of Kearns-Sayre syndrome

Josef Finsterer

Neurology Department, Neurology & Neurophysiology Center, Vienna, Austria.

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Dear Editor,

We were interested to read the article by Amergoolov *et al.* on two patients with Kearns-Sayre Syndrome (KSS) due to single mtDNA deletions who had phenotypic endocrine disorders among other features.[1] Patient 1, a 20-year-old female, was diagnosed with hypogonadism, diabetes and osteoporosis, and patient 2, a 22-year-old male, was diagnosed with impaired glucose tolerance and osteoporosis.[1] It was found that the severity of clinical manifestations increases with the size of the mtDNA deletion, but that other factors such as heteroplasmy, mtDNA duplications or pleioplasmia can also determine the severity of the disease.[1] The study is impressive, but some points should be discussed.

The first point is that the endocrine involvement in KSS is more extensive than described in the article. KSS patients often show developmental delay and short stature early in life.[2] Short stature is usually due to reduced secretion of Somatotropic Hormones (STH) from the pituitary gland. Pituitary insufficiency has previously been diagnosed in these patients.[3] How high were the STH levels in the two index cases? There are also KSS patients with hypothyroidism,[4] hypoparathyroidism,[5] hypocorticism (Addison's disease),[3] hypoadrenalism, pancreatic insufficiency and hypogonadism.[6] Patients with multiple endocrinopathies have also been reported.[7] Therefore, it is recommended to perform a complete hormone panel in these patients, including not only pituitary hormones, but also thyroid, parathyroid, pancreatic, gonadal, renal and adrenal hormone levels.

The second point is that neither patient 1 nor patient 2 had an MRI of the brain including the pituitary gland.[1] In order to assess whether a pituitary apoplexy, adenoma, empty sella or hypophysitis was present, it would have been important that at least the hypothalamus and pituitary gland were examined with contrast in both patients. KSS can also manifest with leukoencephalopathy or basal ganglia calcifications,[8] which is why it is also important to perform a cerebral MRI in both cases.

The third point is that KSS can also manifest with anaemia, leukopenia or thrombocytopenia or even pancytopenia, as in Pearson's bone marrow syndrome. Was there any evidence of involvement of the hematopoietic system in either patient?

The fourth point is that KSS can also be associated with renal insufficiency.[9] Did either patient suffer from renal disease such as Toni-Debre-Fanconi syndrome, renal insufficiency, nephrolithiasis, nephrotic syndrome, renal cysts, renal tubular acidosis, Bartter-like syndrome, focal segmental glomerulosclerosis, tubulointerstitial nephritis, nephrocalcinosis, and benign or malignant neoplasms, as previously reported.[9]

The fifth point is that cardiac involvement in KSS includes not only AV block III, but also several other cardiac abnormalities. These include cardiomyopathy and various supraventricular and ventricular arrhythmias.[10] Screening for ventricular arrhythmias by Holter monitoring is therefore crucial, as ventricular arrhythmias can determine outcome and are usually amenable to treatment.

The sixth point is that heteroplasmy rates have not been reported.[1] Since the phenotype may depend not only on the deletion size but also on the heteroplasmy rate, it is essential to determine this influencing factor. Although KSS is inherited via the maternal trait in only four percent of cases, it is important to report whether the mtDNA deletions found were inherited from the mothers or arose *de novo*.

The seventh point is that the conclusions are only partially justified. It is not justified to conclude from two cases that the severity of the disease increases with the size of the deletion and that other factors of mitochondrial genetics may determine the phenotype.

Finally, it should be explained what is meant by pleioplasmia. Do the authors mean mtDNA copy number or do they mean mtDNA polymorphisms that additionally determine the phenotype?

Overall, this interesting study has limitations that put the results and their interpretation into perspective. Addressing these limitations could strengthen the conclusions and re-

inforce the message of the study. All unanswered questions need to be clarified before readers uncritically accept the conclusions of the study. KSS patients should be systematically and prospectively screened for polyendocrinopathy and for multisystem involvement in the disease. Better powered, multicenter studies are needed before conclusions can be drawn about the relationship between the severity of KSS and mtDNA genetics.

Ethical approval

Not applicable.

Consent to participation

Not applicable.

Consent for publication

Not applicable.

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Conflict of interest

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Corresponding author

Josef Finsterer, Neurology Deartment, Neurology & Neurophysiology Center, Postfach 20, 1180 Vienna, Austria.
Tel. +43-1-5861075 - Fax. +43-1-5861075.
ORCID ID: 0000-0003-2839-7305.
E-mail: fifigs1@yahoo.de

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