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Letter to the Editor

Is Fanconi Syndrome Actually the First Manifestation of Kearns-Sayre Syndrome?

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Letter to the Editor

We read with interest the article by Lu *et al*. on a 10-year-old female patient with Kearns-Sayre syndrome (KSS). It was claimed that Fanconi syndrome was the primary manifestation of KSS due to a heteroplasmic mtDNA deletion of 7521 kb [1]. In addition to Fanconi syndrome, the patient phenotypically exhibited growth retardation since the age of five, short stature, hearing impairment, osteopenia, ptosis, ophthalmoparesis, paraparesis of the lower extremities prior to Fanconi syndrome, and type 1 diabetes [1]. The patient benefited from a mitochondrial cocktail and diabetes treatment [1]. The study is noteworthy, but several points deserve discussion.

First, we disagree with the assertion that Fanconi syndrome was the initial manifestation of the single mtDNA deletion [1]. According to the case report, the patient developed lower extremity paraparesis prior to the diagnosis of Fanconi syndrome [1]. Furthermore, the patient suffered from growth retardation and short stature since the age of five. Since growth retardation in KSS is usually due to pituitary dysfunction with growth hormone deficiency and present already at birth, it is conceivable that this impairment existed prior to the onset of Fanconi syndrome. Therefore, we should know whether birth height and weight were normal.

The second point is that KSS can overlap with Pearson syndrome, which is characterized by pancytopenia and exocrine pancreatic insufficiency [2]. Was there evidence of anemia, leukopenia, or thrombocytopenia in the index patient? Was there evidence of exocrine pancreatic insufficiency and diarrhea?

The third point is that heteroplasmy rates of the detected mtDNA deletion were not reported in either affected or unaffected tissues. Knowledge of heteroplasmy rates is crucial because, in addition to mtDNA copy number, haplotype, and nuclear background, they can also determine the phenotype and disease progression. Since individual mtDNA deletions can also be due to mutations in nuclear genes involved in mtDNA maintenance [3], it would also have been helpful to screen for a mutation in one of these genes by whole exome sequencing.

The fourth point is that family history was not reported [1]. Although single mtDNA deletions are only inherited maternally in 4% of cases [4], we should know whether the mtDNA deletion arose de novo in the index patient or was inherited from the mother. Knowledge of the mutation origin is crucial for assessing genotype-phenotype correlation in a family and for genetic counseling.

The fifth point is that no explanation was given for the metabolic acidosis noted at age three [1]. Was the metabolic acidosis due to elevated serum lactate, Fanconi syndrome, ketoacidosis, or a compensatory response to respiratory acidosis? We should also know whether or not the metabolic acidosis persisted during the further course of the disease. Knowledge of the pathophysiology of acidosis is crucial for optimal treatment of the disease.

The sixth point is that no long-term ECG recordings were performed on the patient [1]. Since patients with KSS can experience not only atrioventricular block but also ventricular arrhythmias [5], the exclusion of malignant ventricular arrhythmias would have been crucial.

The seventh point is that the patient was not prospectively examined for cerebral involvement using MRI before pacemaker implantation. Knowledge of the extent of cerebral involvement is crucial, as it can determine the further course of the disease and outcome [6].

One limitation of the study is that lactate was not measured during the cerebrospinal fluid (CSF) examination. Since CSF lactate can be elevated in KSS, determining CSF lactate would have been useful. Elevated CSF lactate can cause confusion or seizures, so it should be known whether it was elevated or not. Further limitations include the fact that neither all reference values nor the results of EEG recordings were reported [1]. Since epilepsy can manifest in patients with KSS [7], it is crucial to

know whether or not the index patient exhibited paroxysmal activity in the EEG recordings.

Overall, patients with KSS require prospective investigations for multisystem involvement and close follow-up to avoid missing brain or cardiac involvement, which determines outcome and is usually treatable if detected early.

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