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Urinary Organic Acids in Patients with Single mtDNA Deletions

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ABSTRACT

Urinary organic acids can be helpful to diagnose mitochondrial disorders (MIDs). Urinary organic acids are increasingly recognised as a diagnostic biomarker of MIDs. Aim of a recent retrospective study was thus to investigate if the urinary organic acid profile (UOAP) differs between patients with Kearns-Sayre syndrome (KSS), Pearson marrow-pancreas syndrome (PMS), and healthy controls. Semeraro et al. investigated the urinary organic acid profile (UOAP) in 15 patients carrying a single mtDNA deletion. The UOAP was normal in 8 patients with KSS but abnormal in 7 patients with PMS. However, since the study lacks information about the heteroplasmy rates, family history, clinical presentation of the included patients, results about follow-up investigations, and explanations for the variability of the UOAP during follow-up, the presented results have to be interpreted with caution. As long as these issues are not addressed, it cannot be concluded that the UOAP "represents a helpful tool for the diagnosis of PMS".

Keywords: *urine organic acids, hereditary, phenotype, genotype, mtDNA, Pearson syndrome, Kearns-Sayre syndrome, progressive external ophthalmoplegia*

INTRODUCTION

Urinary organic acids (UOA) in particular 3-hydroxybutyrate, 3-hydroxyisobutyrate, fumarate, pyruvate, 2-hydroxybutyrate, 2-ethyl-3-hydroxypropionate, and 3-methylglutaconate, can be helpful to diagnose mitochondrial disorders (MIDs) particularly in areas where the economic burden and absence of specialized centers limits the diagnosis.[1] UOA are abnormal in up to 80% of the patients with a MID.[2] UOA are thus increasingly recognised as a diagnostic biomarker of MIDs and applied with increasing frequency for diagnostic purposes. Aim of a recent retrospective study by Semeraro et al.[3] was thus to investigate if the urinary organic acid profile (UOAP) differs between patients with Kearns-Sayre syndrome (KSS), Pearson marrow-pancreas syndrome (PMS), and healthy controls.

METHODS

In a retrospective single-center study the UOAP was determined in 15 patients with single large-scale mtDNA deletions.[3] Included were 8 patients with KSS and 7 patients with PMS. Twenty-five age-matched healthy subjects served as a control group. Twelve organic acids were determined by routine diagnostic methods in the urine of these patients.

RESULTS

Clinical characteristics of PMS and KSS patients were provided in table 1 of Semeraro's study.[3] In the 7 patients with PMS age at follow-up ranged between 0.5 and 11.5 years. Six of seven patients presented with growth retardation, 4 of 7 patients with neurological abnormalities, 7 of 7 patients with hematological abnormalities, 5 of 7 patients had renal insufficiency, 3 of 7 patients had cardiac involvement, 7 of 7 patients presented with endocrine abnormalities, and 6 of 7 patients with gastrointestinal disease.[3] Except for one patient, 6 of 7 patients had died already at ages 0.5 to 12.5 years.[3] Among the 8 patients with KSS, age at follow-up ranged between 11 and 18 years. Seven of eight patients presented with growth retardation, 8 of 8 patients with neurological abnormalities, 1 of 8 patients with hematological abnormalities, 2 of 8 patients had renal insufficiency, 7 of 8 patients presented with cardiac involvement, 6 of 8 patients had endocrine abnormalities, 6 of 8 patients gastrointestinal disease, and 5 of 7 patients presented with psychiatric peculiarities.[3] All KSS patients were still alive. The UOAP was abnormal in all patients with PMS but normal in most patients with KSS as indicated in figure 1 of Semeraro's study.[3] Useful novel metabolites of the UOAP that discriminated between

controls and PMS patients included 3-methylglutarate, triglylglycine, and 2-methyl-2,3-dihydroxybutyrate.

DISCUSSION

Semeraro et al. found elevated UOA in patients with PMS but normal UOA in patients with KSS.[3] The variable results between patients with KSS and PMS were attributed to a higher tissue expression of mtDNA deletions in PMS than in KSS.[3] It is well established that different tissue distribution of mtDNA deletions in single large-scale mitochondrial DNA deletion disorders represents a critical determinant of the phenotype.[4] However, the variable UOAP between KSS and PMS patients may have other causes as well. Single mtDNA deletions in KSS and PMS occur in a heteroplasmic pattern, which is the ratio between mutated and wild-type mtDNA. Heteroplasmy is strongly dependent on the tissue where it is determined. Heteroplasmy rates may strongly influence the phenotype. Thus, it would be interesting to know if the heteroplasmy rates in hair follicles, buccal mucosa, muscle, lymphocytes, fibroblasts, and urinary epithelial cells were different between KSS and PMS patients.

The phenotype of a single mtDNA deletion syndrome is not only dependent on the heteroplasmy rate but also on the size and the location of the deletion within the mtDNA ring.[5] Size of mtDNA deletions ranges from 1000 to 10000 bp.[6] Thus, we should be informed if there was a difference in the mean size of the tDNA deletions between KSS and PMS patients and if the UOAP correlated with the size of the mtDNA deletion in the 15 investigated patients. The authors should also provide the location of the deletions within the mtDNA ring and which of mtDNA genes were deleted.

Interestingly, 6 of 7 PMS patients had growth retardation, 4 of 7 patients had neurological impairment, 3 of 7 patients cardiac involvement, 7 of 7 patients endocrine involvement, and 5 of 7 patients renal involvement. Thus, the phenotype was hardly different between PMS and KSS patients and it should be explained why the PMS patients with multisystem involvement were classified as PMS and not as KSS Which neurological, cardiac, renal, endocrine, or gastrointestinal abnormalities were found in PMS patients and which in PMS patients? Which phenotypic features differed between the two groups?

The authors also found that 3-methyl glutaconic aciduria (3MGA) was associated with increased excretion of 3-methyl glutaric acid.[3] They mention that 3MGA and increased excretion of 3-methyl glutaric acid may not only occur in patients carrying mtDNA deletions but also in patients carrying mutations in the *TAZ*, *OPA3*, *TMEM70*, or *SERAC1* genes respectively.[3] However, 3MGA with increased excretion of 3-methyl glutaric acid has been also reported in patients with Alexander disease, which is due to mutations in *GFAP*,[7] in patients with 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) lyase deficiency,[8] and in patients misdiagnosed with cerebral palsy.[9] Thus, 3MGA is a non-specific finding and cannot serve as a biomarker of disorders associated with mtDNA deletions.

The authors also mention that PMS patients who survive into adulthood develop a KSS phenotype.[3] From this statement and the current findings of the study we can infer that the UOAP should normalize with progression to KSS. However, the opposite was the case and the three patients who developed a KSS phenotype had an UOAP even more abnormal than in the PMS stage and no sufficient explanation for this unexpected finding was provided.

According to table 2 in Semeraro's study,[3] three patients had follow up investigations of the UOAP.[3] Urine lactate and 3HIB decreased over time in these three patients, but the other UOA showed an inconclusive trend. It would be interesting to know the reason for the continuous lactate and 3HIB decease over time. Why was there no continuous trend visible for the other UOA? The inconclusive trend over time excludes these two parameters as biomarkers for mtDNA deletion disorders.

Though MIDs due to single mtDNA deletions are sporadic in the majority of the cases, transmission via the maternal line can be observed in about 4% of the cases.[10] Thus, it would be useful to know in how many of the 15 patients the family history was positive for KSS or PMS or phenotypic features present suggesting a MID. Was the UOAP determined in any of the first degree relatives of the 15 included patients? Did any of first degree relatives of the included patients undergo genetic work-up for the presence or absence of mtDNA mutations?

In a previous study of four patients with PMS, one patient presented with an abnormal UOAP.[11] In this patients the 3-hydroxyisobutyric acid was elevated in the urine.[11] The patient also had low levels of

citrulline and arginine despite normal ammonia levels.[11] The authors found that the conversion of ornithine to citrulline, which is catalysed by ornithine transcarbamylase, might not be very efficient in PMS patients. The authors speculated that ammonia and carbamyl-phosphate could be diverted from the urea cycle for the synthesis of nucleotides.[11] Thus, we should be informed if ammonia and amino acid levels were normal or decreased.

Since de novo mtDNA deletions may also present with corneal clouding due to corneal dystrophy in addition to Fanconi syndrome,[12] it would be interesting to know if any of the included patients had visual problems and how many of the 15 patient had Fanconi syndrome (proximal renal tubular dysfunction).[12]

CONCLUSIONS

In summary, the interesting retrospective study by Semeraro et al. lacks information about the heteroplasmy rates, family history, and the clinical presentation of the included patients. It could be useful to provide follow-up investigations and explanations for the variability of the organic acids during follow-up. As long as these issues are not addressed, the current conclusions of the study should be revised.

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