Mitochondrial Neurogastrointestinal Encephalomyopathy Causing Fanconi Syndrome

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Received 6 July 2022; revised 25 July 2022; accepted 26 July 2022; published online 5 August 2022

Kidney Int Rep (2022) 7, 2534–2536; https://doi.org/10.1016/j.ekir.2022.07.176
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INTRODUCTION

Mitochondrial neurogastrointestinal encephalopathy (MNGIE) is a rare autosomal recessive disorder due to TYMP mutations that cause thymidine phosphorylase deficiency, leading to mitochondrial DNA depletion, deletions, and point mutations that, in turn, cause mitochondrial dysfunction. Most commonly, MNGIE manifests in gastrointestinal and neurological dysfunction with severe and progressive gastrointestinal dysmotility, cachexia, chronic progressive external ophthalmoplegia, leukoencephalopathy, and sensorimotor peripheral neuropathy.1 To date, renal manifestations in MNGIE have not been described in the literature. Nevertheless, in other mitochondrial disorders, such as Kearns-Sayre syndrome and Leigh syndrome, the most frequent renal manifestation is partial or general proximal tubular dysfunction.2 Herein, we present a report about a young woman with MNGIE who developed Fanconi syndrome.

CASE PRESENTATION

A 26-year-old woman with genetically confirmed MNGIE presented to our hospital with pneumonia. She developed recurrent abdominal pain at age 7 years and at 17 years, she had a jejunal perforation presumed to be due to a foreign body. At age 19 years, during an evaluation for cachexia and vomiting, brain magnetic resonance imaging revealed leukoencephalopathy. Clinical genetic testing confirmed compound heterozygous TYMP gene mutations (c.729delC and c.977G>A). A first cousin was also diagnosed with MNGIE. Our patient’s course was severe with recurrent hospital admissions owing to pneumonias, urinary tract infections, and gastrointestinal dysfunction. At age 17 years, she became bedbound due to neuropathy complicated by joint contractures and developed severe weight loss from 76 pounds at age 17 years to a nadir of 50 pounds at age 26 years. She was fully dependent on home parenteral nutrition (PN) support. She developed deafness, ptosis, ophthalmoplegia, and partial blindness but remained cognitively intact and communicated via writing.

She was admitted at the end of 2021 to our institution with pneumonia as well as pleural and pericardial effusions. She was treated for pneumonia with antibiotics. Thoracentesis revealed a transudative pleural effusion. Laboratory values upon presentation are presented in Table 1. Several metabolic abnormalities were noted on serum and urine examination. These included a mildly low serum bicarbonate, a highly basic urine (pH 9), low serum uric acid level and normoglycemic glycosuria. Further investigation (Table 2) revealed elevated fractional excretion of phosphorus and uric acid, as well as the presence of high levels of nonalbumin proteinuria. Taken together, this constellation of findings was diagnostic of Fanconi syndrome. She had not taken any medications typically associated with Fanconi syndrome such as antineoplastic agents, tenofovir and had a negative Sjogren antibody screen. Her serum and urine protein electrophoresis were negative for monoclonal gammopathy.
Table 1. Patient’s initial laboratory values

| Serum test                        | Result | Reference range |
|-----------------------------------|--------|-----------------|
| White blood cell count, ×10⁹/μl    | 6      | 3.12–8.44       |
| Hemoglobin, g/dl                  | 8.9    | 12.6–17.0       |
| Platelet count, ×10⁹/μl           | 83     | 156–325         |
| Sodium, mmol/l                    | 137    | 137–145         |
| Potassium, mmol/l                 | 4.5    | 3.5–5.1         |
| Chloride, mmol/l                  | 103    | 96–107          |
| Bicarbonate, mmol/l               | 21     | 19–27           |
| Serum urea nitrogen, mg/dl        | 23     | 7–26            |
| Creatinine, mg/dl                 | 0.34   | 0.70–1.30       |
| Calcium, mg/dl                    | 8.7    | 8.8–10.3        |
| Magnesium, mg/dl                  | 1.9    | 1.6–2.6         |
| Phosphorus, mg/dl                 | 3.3    | 2.5–4.5         |
| Serum glucose, mg/dl              | 77     | 75–100          |
| Albumin, g/dl                     | 2.7    | 3.9–5.2         |
| Uric acid, mg/dl                  | 8.6    | 3.0–7.1         |
| Cystatin C, mg/dl                 | 1      | 0.5–1.2         |
| Venous pH                         | 7.40   | 7.36–7.41       |
| pCO₂, mmHg                        | 38     | 40–45           |
| Lactate, mmol/l                   | 3.4    | 0.5–2.2         |
| Urine test                         | x      |                 |
| pH                                | 8      | 5–8             |
| Glucose, mg/dl                    | 500    | 0               |
| Protein, mg/dl                    | 56     |                 |
| Albumin, mg/dl                    | 9.2    |                 |
| Urine albumin/protein ratio        | 0.16   |                 |

DISCUSSION

MNGIE is caused by TYMP mutations that results in thymidine phosphorylase deficiency. The effect of this mutation is accumulation of thymidine and deoxyuridine, which result in unbalanced deoxynucleoside triphosphate pools that impair replication of mitochondrial DNA. Reported cases of MNGIE are rare, and as of 2011, only 200 cases have been reported in medical literature.

MNGIE is characterized by gastrointestinal hypomotility resulting in dependence on PN. Other characteristics include ptosis, and progressive deafness and blindness. It is also characterized by severe muscle wasting and unresponsive to nutritional interventions. Moreover, it is believed that over-nourishment hastens the development of these characteristic abnormalities.

Overall, prognosis is poor with average life expectancy of 37 years. Treatment with hematopoetic stem cell and liver transplantation or erythrocyte-encapsulated thymidine phosphorylase have decreased plasma levels of thymidine and deoxyuridine and have ameliorated clinical symptoms but pose risks of morbidity and mortality in patients who are often physically frail from the disease. Patients with MNGIE often require early and recurrent surgical intervention for diverticulitis and intestinal dysmotility with considerable morbidity.

Our patient had the hallmark features of MNGIE, including early onset, leukoencephalopathy, ophthalmoplegia, progressive gastrointestinal dysmotility, and cachexia; however, the progression of neurological and gastrointestinal dysmotility with early dependence on PN was more rapid than typical cases.

An atypical aspect of her presentation was her generalized proximal tubular dysfunction. A highly metabolic region of the kidney, the proximal tubule is responsible for reabsorbing roughly 70% of the glomerular filtrate, comprising about 150 liters of volume. The reabsorption of most of the water, sodium, phosphorus, uric acid, glucose, amino acids, and small molecular weight proteins occur in the proximal tubule. The proximal tubule’s reabsorption capacities are tied to ion and amino acid channels, which require a Na⁺/K⁺-ATPase for their respective electrochemical gradients. Notably, the proximal tubule has a higher density of mitochondria than anywhere else in the kidney, which are necessary to power its metabolic work.

In addition, the proximal tubules are uniquely reliant on aerobic respiration for adenosine triphosphate (ATP) production due to their lack of capacity to synthesize ATP anaerobically from glycolysis.

Our patient exhibited many of the cardinal features of Fanconi syndrome. Her serum uric acid was quite low, with a very elevated fractional excretion of uric acid. She exhibited an elevated fractional excretion of phosphorus and her normal serum level was likely maintained by high levels of parenteral phosphorus added to the PN. She had nonalbumin proteinuria, with only 16% of her urine protein content being due to albumin. The finding of albumin comprising less than 40% of total urine protein suggests tubular rather than glomerular proteinuria.

Further, she exhibited marked normoglycemic glycosuria, suggesting proximal tubular inability to reabsorb glucose.

Table 2. Assessment of proximal tubular function

| Laboratory value | Serum concentration | Urine concentration | Fractional excretion | Normal fractional excretion |
|------------------|---------------------|---------------------|----------------------|-----------------------------|
| Creatinine, mg/dl| 0.34                | 13.1                | NA                   | NA                          |
| Phosphorus, mg/dl| 3.3                 | 54.4                | 43%                  | 5–15%                       |
| Uric acid, mg/dl | 0.6                 | 20.2                | 87%                  | 10%                         |
| Glucose mg/dl    | 77                  | 500                 | 17%                  | 0 (if serum glucose below 180 mg/dl) |
| Bicarbonate mmol/l| 21                  | 190 (calculated using Henderson Hasselbach equation using pCO₂ of ~80) | 21% | 0 |

NA, not available.
It should be noted that her serum levels of bicarbonate were only mildly low, which is unexpected in the presence of proximal tubular bicarbonate wasting. In addition, her urine pH was quite basic, which is unusual in a proximal renal tubular acidosis. This can be explained by considering the composition of her PN prescription. She had been receiving increasing amounts of base in the form of acetate in her PN. Eight months prior to hospitalization, she was receiving 250 mEq daily of acetate, and by the time of hospitalization she required 335 mEq of acetate daily. This large administration of base explains why her bicarbonate level was only mildly depressed despite significant proximal tubular dysfunction. This also explains why her urine pH was quite basic, because she had ongoing bicarbonate loss due to her plasma bicarbonate level continually remaining above the reabsorption threshold for her proximal tubule. It is likely that her proximal tubular dysfunction would have been detected earlier were it not for the fact that her lost electrolytes (bicarbonate, phosphorus, and glucose) were being constantly supplemented via PN. A comprehensive screening for proximal tubulopathy in patients with MNGIE may reveal a large proportion affected, that are simply masked by administration of PN.

Though Fanconi syndrome has not been reported in MNGIE, there is ample reason to suspect that her underlying mitochondrial disease was the cause of MNGIE. In similar mitochondrial disorders that exhibit leukodystrophy and gastrointestinal disease, such as Kearns-Sayre syndrome and Leigh syndrome, the most frequently reported renal abnormality is Fanconi syndrome. In addition, in this patient, other causes of Fanconi syndrome such as culprit medications, paraproteinemia, and autoimmune disorders were excluded. It is possible that renal manifestations are under-recognized in MNGIE due to the severity and rapid morbidity of other organs’ involvement that are usually the focus of clinical care, as well as the frequent reliance on PN, which can mask the more obvious metabolic abnormalities.

### Table 3. Teaching Points

| MNGIE and the kidney |
|----------------------|
| MNGIE is a mitochondrial disorder characterized by gastrointestinal hypomotility, leukoencephalopathy, muscle wasting and ophthalmoplegia. These patients often require parenteral nutrition and usually have a progressive course. |
| Proximal tubular dysfunction is a common renal manifestation of mitochondrial disease. Fanconi syndrome can occur in MNGIE and electrolyte abnormalities may be masked by the administration of parenteral nutrition. |

MNGIE, mitochondrial neurogastrointestinal encephalopathy.

### CONCLUSION

Though proximal tubular dysfunction has been reported in other mitochondrial disorders, to our knowledge, this is the first report of Fanconi syndrome in MNGIE. Clinicians should be cognizant of this manifestation of MNGIE and should monitor for and correct resultant electrolyte disturbances (Table 3).

### DISCLOSURE

All the authors declare no competing interests.

### PATIENT CONSENT

We thank the patient for consenting to present her case in the medical literature. We are sad to report that the patient passed away from multiple complications due to the disease prior to publication of this report. This report is published in her memory and with the hope that it will help future clinicians diagnose and treat patients with MNGIE.

### ACKNOWLEDGMENT

We thank Dr. Qais Al-Awqati, who reviewed the manuscript and guided the authors through the physiology of this case.

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