ACID-BASE AND ELECTROLYTE TEACHING CASE

Acute Tubular Dysfunction With Fanconi Syndrome: A New Manifestation of Mitochondrial Cytopathies

François-Guillaume Debray, MD,[1] Aicha Merouani, MD,[2] Marie Lambert, MD,[1] Pierre Brochu, MD,[3] Chantal Bernard, MD,[4] Brian H. Robinson, PhD,[5] and Grant A. Mitchell, MD[1]

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Mitochondrial diseases are a heterogeneous group of energy metabolism disorders that can affect almost any organ.[1] Kidney disease is well-known in patients with mitochondrial disorders, most commonly manifesting as proximal tubulopathy with chronic tubular acidosis, typically a minor feature in pediatric patients with severe involvement of brain, liver, heart, or other organs.[2-5] Other renal presentations include chronic tubulointerstitial nephropathy,[6,7] progressive glomerular diseases,[8,9] and nephrotic syndrome.[10] Acute, severe, and fluctuant tubular dysfunction has not been previously described.

CASE REPORTS

Clinical Histories

Patient 1

A girl born to first-cousin Turkish parents was admitted at age 2 weeks for failure to thrive, tachypnea, and fever. Blood chemistry results were as follows: pH, 7.07; P_{CO_2}, 57.6 mm Hg; bicarbonate, 16 mEq/L (mmol/L); anion gap, 16 mEq/L (mmol/L); lactate, 74 mg/dL (8.27 mmol/L; normal, <20 mg/dL); and lactate-pyruvate molar ratio, 41.9 (normal, <17). She received antibiotics for suspected sepsis. Acid-base status thereafter normalized. Plasma phosphorus level was 6.9 mg/dL (2.3 mmol/L), and tubular reabsorption of phosphate was 91%. The patient was readmitted at 4 months for fever. Blood chemistry showed pH of 7.19; P_{CO_2} of 43.2 mm Hg; bicarbonate of 15.3 mEq/L (mmol/L); anion gap of 10.1 mEq/L (mmol/L); and lactate level of 17.7 mg/dL (1.97 mmol/L). Urinary pH was 6.0 and glycosuria was absent. Renal tubular acidosis was suspected and bicarbonate was administered. Psychomotor delay and neurosensory deafness were documented, and she required nasogastric tube feeding.

Because of multisystemic involvement, a mitochondrial disease was suspected, and at 7 months, the patient was electively admitted for investigations. Blood analyses showed the following values: pH, 7.33; P_{CO_2}, 39 mm Hg; bicarbonate, 22.0 mEq/L (mmol/L); and anion gap, 12.0 mEq/L (mmol/L). Urinary pH was 8.0, and there was generalized aminoaciduria without glycosuria (Fig 1A). Plasma phosphorus level was 3.3 mg/dL (1.10 mmol/L; normal, 1.45 to 2.1 mmol/L), and tubular reabsorption of phosphate was 72%. Muscle biopsy results were normal, but liver showed marked mitochondrial proliferation and ultrastructural anomalies.

At 1 year, the patient was readmitted for fever. Blood analysis results were as follows: pH, 7.35; P_{CO_2}, 26.2 mm Hg; bicarbonate, 14.4 mEq/L (mmol/L); anion gap, 15.6 mEq/L (mmol/L); and lactate, 40 mg/dL (4.44 mmol/L). Urinary pH was 6.0, and glycosuria showed glucose of 252 mg/dL (14 mmol/L). Bicarbonate administration was transiently doubled. Two weeks later, electrolyte imbalances resolved, and she returned to her previous level of bicarbonate supplementation. At this age, renal investigations repeatedly showed generalized aminoaciduria, normoglycemic glycosuria (glucose, 180 mg/dL [10 mmol/L]), proteinuria (protein, 0.12 g/dL [1.19 g/L]), hypophosphatemia (phosphate, 1.5 mg/dL [0.5 mmol/L]), low tubular reabsorption of phosphate (52%), hypercalciuria (urinary calcium-creatinine ratio, 5.96), and mild nephrocalcinosis. Blood pH was 7.31, plasma bicarbonate level was 19 mEq/L (mmol/L), and urinary pH was 7.0. Plasma creatinine level was 0.2 mg/dL (18 μmol/L), and glomerular filtration rate measured by using creatinine clearance was 110 mL/min/1.73 m^2 (1.83 mL/s/1.73 m^2). Phosphorus was administered.

At 15 months, another major metabolic crisis occurred. Initial laboratory values were pH, 7.11; P_{CO_2}, 31 mm Hg; bicarbonate, 11 mEq/L (mmol/L); anion gap, 14 mEq/L (mmol/L); lactate, 62 mg/dL (6.88 mmol/L); and urinary pH, 7.0. Bicarbonate requirements increased 10-fold (to 22 mEq [mmol]/kg/d intravenously), and phosphorus, to 95 mg/kg/d (Fig 2A). Glycosuria exceeded 1 g/L (>55 mmol/L). Unexpectedly, tubular losses improved and all electrolyte supplements were stopped within 5 weeks. For 5 additional weeks, mean plasma bicarbonate and phosphorus concentrations

From the Divisions of [1]Medical Genetics and [2]Nephrology, Department of Pediatrics; and [3]Department of Pathology, CHU Sainte-Justine; [4]Department of Pathology, Montreal Children Hospital, McGill University, Montreal, Québec; and [5]Metabolism Research Program, Research Institute, Department of Pediatrics and Biochemistry, The Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada.

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Address correspondence to Grant A. Mitchell, MD, CHU Sainte-Justine, 3175 Côte Sainte-Catherine, Montréal, Québec, H3T 1C5, Canada. E-mail: grant.mitchell@recherche-ste-justine.qc.ca

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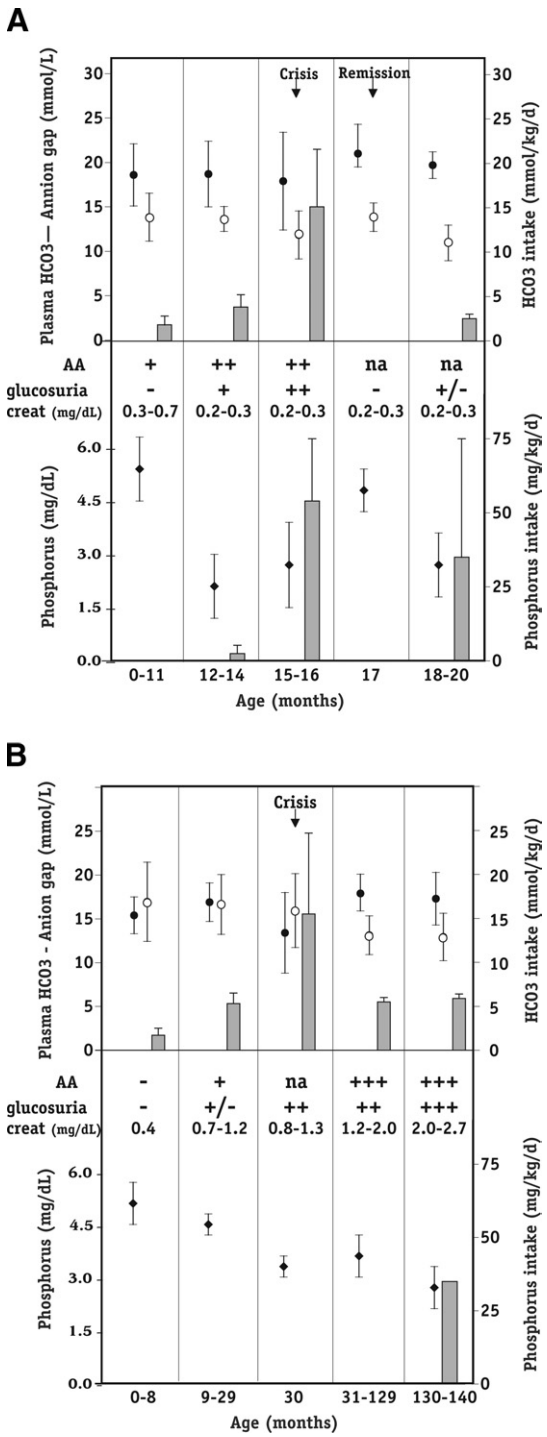
were 24.8 ± 1.9 (SD) mEq/L (mmol/L) and 5.1 ± 0.3 mg/dL (1.7 ± 0.1 mmol/L), respectively. Glycosuria disappeared. Hypophosphatemia and acidosis recurred thereafter, with intermittent glycosuria (glucose, 0 to 100 mg/dL [0 to 5 mmol/L]), and supplementations were reintroduced (Fig 1A).



The patient had severe encephalopathy and developed hypsarrhythmia and sideroblastic anemia requiring multiple transfusions.

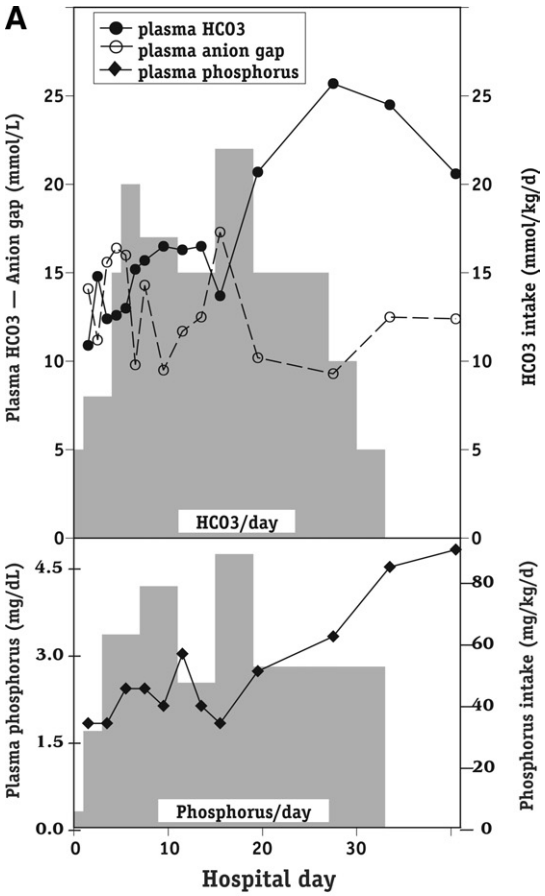
At 21 months, the patient was admitted for vomiting and fever and rapidly developed profound metabolic acidosis uncontrolled by bicarbonate infusion. Lactic acidemia increased to 315 mg/dL (35 mmol/L), and she died of multiple organ failure. Autopsy included muscle and kidney biopsies performed 1 hour postmortem. Muscle was normal, but proximal tubular cells showed massive mitochondrial proliferation (Fig 3A).

Patient 2

This girl born to unrelated French-Canadian parents at 35 weeks of gestation was admitted at age 2 months for irritability and poor weight gain. Blood analysis showed the following values: pH, 7.42; P_{CO_2}, 26 mm Hg; bicarbonate, 17.0 mEq/L (mmol/L); anion gap, 11 mEq/L (mmol/L); lactate, 70 mg/dL (7.73 mmol/L), and lactate-pyruvate ratio, 40.6. Glycosuria and aminoaciduria were absent. Nasogastric tube feeding was introduced and bicarbonate was administered (Fig 1B). At age 9 months, serum creatinine level was 0.73 mg/dL (65 μmol/L), and isotopic glomerular filtration rate was 42 mL/min/1.73 m^2 (0.70 mL/s/1.73 m^2). Urinalysis showed normoglycemic glycosuria (glucose, 100 mg/dL [5.5 mmol/L]), proteinuria (protein, 0.63 g/L), pH of 7, and generalized aminoaciduria. Plasma phosphorus concentration was normal (4.5 mg/dL [1.50 mmol/L]), and plasma bicarbonate level was 20 mEq/L (mmol/L). Renal biopsy at 9 months, normal by means of light microscopy, showed mitochondrial proliferation and abnormalities by electron microscopy in proximal tubular cells (Fig 3B). During the following months, bicarbonate supplementation was increased to 7 mEq (mmol)/kg/d, but growth remained impaired. She walked unaided at 16 months and language development was normal.

At 30 months, the patient presented with a severe acidotic crisis requiring continuous intravenous bicarbonate infusion (up to 33 mEq [mmol]/kg/24 h) for nearly 1 month (Fig 2B). At admission, she was polypneic and mildly dehydrated (weight loss $< 3\%$). Laboratory values were as follows: pH, 7.07; P_{CO_2}, 26.9 mm Hg, bicarbonate, 3.3 mEq/L (mmol/L); lactate 195 mg/dL (21.7 mmol/L); anion gap, 23.7 mEq/L (mmol/L); and glucose, 150 mg/dL (8.3 mmol/L). Urinalysis showed pH 5.0, glycosuria with glucose of 252 mg/dL (14 mmol/L), and proteinuria with protein of 0.10 g/dL (1 g/L). There were no neurological signs, and after an initial period of hydration and bicarbonate infusion, she appeared clini-

Figure 1. Lifelong course of patients (A) 1 and (B) 2. Boxes represent mean for bicarbonate (upper right-side y-axis) and elemental phosphorus (lower right-side y-axis) administrations, mean plasma bicarbonate (closed circle; upper left-side y-axis), mean anion gap (open circle; upper left-side y-axis), and mean plasma phosphorus (closed diamond; lower left-side y-axis). Error bars are SD. Abbreviations: AA, aminoaciduria; creat, plasma creatinine. To convert creatinine in mg/dL to μmol/L, multiply by 88.4; phosphorus in mg/dL to mmol/L, multiply by 3.01.



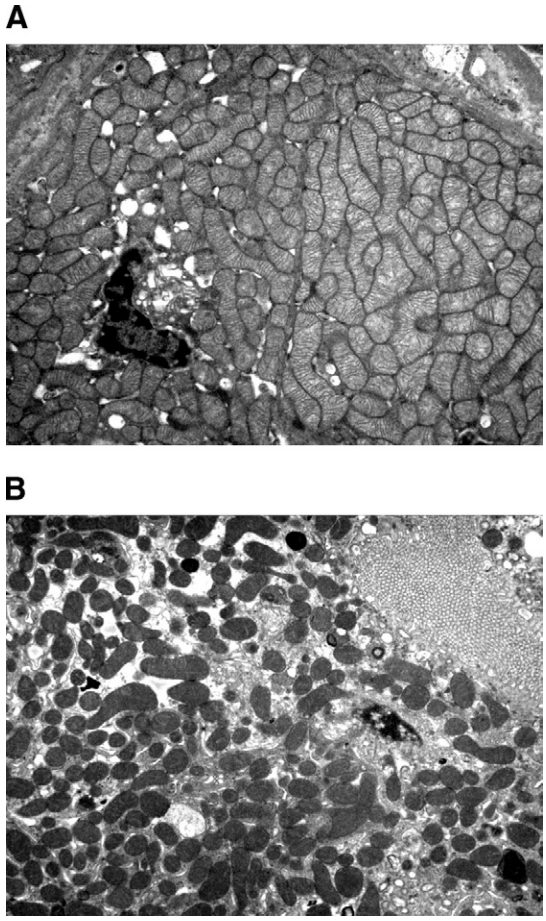


Figure 3. Electron micrographs show widespread proliferation of mitochondria with bizarre shape and hypertrophic cristae occupying most of the volume of proximal tubular cells. (A) Patient 1 (original magnification ×3,000); (B) patient 2 (original magnification ×2,800).

cally well, energetic, and in no distress. Bicarbonate administration was progressively decreased over 4 weeks to 6 mEq (mmol)/kg/d orally. She had a milder acidotic episode at age 4 years, but none thereafter. Chronic renal failure has progressively developed (Fig 1B). In the last 6 months, plasma phosphorus level decreased, with tubular reabsorption of phosphate of 50% and radiological evidence of early rickets. At 11 years, renal evaluation shows proteinuria with protein

Figure 2. Chronology of biological parameters and electrolyte administration during acidotic episodes of patients (A) 1 and (B) 2. Grey boxes show supplementation levels for bicarbonate (upper right-side y-axis) and phosphorus (lower right-side y-axis). Shown are plasma bicarbonate (closed circle; upper left-side y-axis), anion gap (open circle; upper left-side y-axis), and plasma phosphorus (closed diamond; lower left-side y-axis). To convert phosphorus in mg/dL to mmol/L, multiply by 3.01.

of 0.15 g/dL (1.48 g/L), massive aminoaciduria and glycosuria (glucose > 1 g/L), plasma creatinine level of 2.34 mg/dL (207 μmol/L), and creatinine clearance of 29.2 mL/min/1.73 m^2 (0.03 mL/s/1.73 m^2). She receives phosphorus and 1,25-hydoxyvitamin D_3. Of note, development and neurological examination findings are normal.

Additional Investigations

Respiratory chain enzyme activities were measured in fibroblasts and liver as reported.[11,12] Blue native gel studies were performed in fibroblast and liver, as described.[13] Spectrophotometric assays showed complex IV deficiency in the liver of patient 1 (0.2 μmoles of reduced cytochrome c per gram of wet weight tissue per minute; controls, 0.6 to 2.4). Blue native gel studies confirmed decreased levels of complex IV in the liver of patient 1 and showed deficiency of complex I in fibroblasts of patient 2 (not shown).

Clinical Follow-up

Metabolic parameters and tubular function were assessed from the patients' medical charts. The clinical course was divided into periods during which parameters of tubular function remained constant, shown in Fig 1. Major changes in treatment, such as initiation or cessation of electrolyte supplementation, were used to define new periods. Acute acidotic episodes are presented chronologically (Fig 2).

DISCUSSION

Both patients fulfilled the diagnostic criteria of Fanconi syndrome: aminoaciduria, normoglycemic glycosuria, chronic tubular acidosis, and impaired renal phosphate reabsorption. In stable periods, when the patients were acidotic, urinary pH was appropriate for the level of acidosis, indicating preserved distal tubular acidifying capacity. Conversely, in other instances, alkaline urine was observed with normal plasma bicarbonate levels, suggesting a proximal origin of tubular acidosis. In addition to chronic tubulopathy, both experienced major acidotic crises requiring massive bicarbonate administration (up to 22 and 33 mEq/kg/d). Without consideration of renal function, such episodes might falsely be attributed solely to hyperlactatemia. Although lactic acid levels increased during episodes and contributed to the metabolic acidosis, anion gaps remained normal or only modestly increased, indicating that in the absence of digestive losses, acidosis most probably was related to renal tubular dysfunction. Taken together with other signs of proximal tubulopathy, the huge amount of bicarbonate required to maintain acid-base equilibrium and observation of alkaline urine at admission of crisis in patient 1 suggest that acidotic crises were caused by renal bicarbonate losses. In patients with mitochondrial diseases, tubulopathy is often considered a biological marker of little clinical significance, but this report shows that acute tubular failure can be life threatening.

In patients with Fanconi syndrome, tubular losses generally are considered fairly constant.[14] In addition to acidotic crises, patient 1 had transient phosphaturia and glycosuria that resolved in parallel with the tubular acidosis. Patient 2 presented with very late-onset hypophosphatemic rickets, unusual in patients with Fanconi syndrome and particularly surprising regarding her chronic renal failure. Mitochondrial diseases should be considered in patients with atypical Fanconi syndromes and unexplained multiple tubular dysfunctions.

The reported spectrum of renal disease in patients with mitochondrial diseases is listed in Table 1, with usual age at presentation, occurrence of extrarenal symptoms, and biochemical or molecular findings. End-stage renal failure is rare in patients with mitochondrial diseases. In 39 patients with mitochondrial disease and tubulopathy, only 2 had moderate renal failure.[2] In another prospective study, none of 35 patients had serum creatinine levels greater than 0.8 mg/dL (>71 μmol/L).[5] Chronic renal failure was described in a patient with mitochondrial diseases and tubulointerstitial nephritis without tubulopathy.[7] Mitochondrial DNA mutations can cause segmental glomerulosclerosis,[8] leading to end-stage renal failure.[9] In these cases, renal insufficiency manifested later than in our patient 2, and without tubulopathy. The kidney biopsy of patient 2 was performed at age 9 months, and her current glomerular histological state is unknown. Patient 2 shows that mitochondrial diseases can present as a primary renal disease without neurological, hepatic, or cardiac involvement. She also shows that chronic renal failure, rare in patients with mitochondrial diseases, can become the major problem of some patients.

The pathophysiological characteristics of acute tubular dysfunction are unclear, but several observations may be pertinent. Proximal tubules have a high metabolic rate, generating more than 95% of their adenosine triphosphate by means of oxidative metabolism.[19] Recent in vitro experiments showed that nephrotoxicity of some drugs

Table 1. Renal Manifestations of Mitochondrial Disorders

Kidney Involvement	Age	Extrarenal Symptoms	Biochemical/Molecular Diagnosis	Reference
Tubulopathy				
Renal tubular acidosis or Fanconi syndrome	I, C	Neurological disease, multivisceral involvement	Numerous isolated respiratory chain deficiencies (complexes I, II, III, IV)	1-5
	I	Neurological and liver disease	Complex III deficiency, *BCS1L* mutation	15
	I, C	Neurological disease	Complex IV deficiency, *COX10* mutation	16
	I	Sideroblastic anemia, exocrine pancreas dysfunction	Pearson marrow syndrome (mtDNA large deletion)	17
	Adol	Neurological disease, pigmentary retinopathy, cardiopathy (heart block)	Kearns Sayre syndrome (mtDNA large deletion)	2
Tubulointerstitial nephropathy	C, Adol	None or late-onset neurological disease	Mt DNA large deletion	6,7
Glomerulopathy				
Segmental glomerulosclerosis	Adol, adult	None or deafness, diabetes, MELAS syndrome	MtDNA point mutation (AC_000021.2:3243G>A)	8,9
Glomerulosclerosis, nephrotic syndrome	(I), C, Adol	Neurological and multivisceral disease	MtDNA deletion, complex III and CoQ10 deficiency, multiple complex deficiencies	4,18,23
Congenital nephrotic syndrome	NN, I	Progressive neurological disease, cardiomyopathy	Single or multiple respiratory chain deficiencies	10

Abbreviations: Adol, adolescence; C, childhood; I, infancy; MELAS, mitochondrial encephalomyopathy, lactic acidosis, stroke like episodes; mtDNA, mitochondrial DNA mutation; NN, neonatal period.

is related to inhibition of mitochondrial respiration, producing adenosine triphosphate depletion and secondary tubular damages.[20] Functional coupling between ion transport and aerobic respiration was demonstrated in vitro.[21] Moreover, even in normal proximal tubule cells, physiological energy demand is close to the capacity for adenosine triphosphate generation, shown by the rapid decrease in adenosine triphosphate level after stimulation of epithelial sodium transport.[22] This constant dependence of proximal tubular cells on high levels of energy supply resembles that of the central nervous system. Acute neurological crises, termed "metabolic stroke," are well-known in patients with mitochondrial diseases and may be related to imbalance between energy requirement and production, leading to cell death. Of note, metabolic strokes in patients with mitochondrial diseases occur after such stresses as minor infections, during which metabolic demands are presumably increased, compromising energy homeostasis in tissues with impaired energy production capacity. Perhaps the episodes of acute tubular dysfunction in our patients fall within a similar framework.

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