Initiated in 1966, the nephrology training program at Brown University consists of a first year of clinical training followed by a second year primarily devoted to research. The program is designed to prepare fellows for careers in academic medicine and/or primary nephrology care. Trainees interested in additional training may apply for a third year of laboratory research or for a combined clinical/research year in critical care and nephrology that confers eligibility in both subspecialties. The Renal Division includes seven full-time and nine voluntary faculty members and recruits three fellows each year.

The clinical experience covers all aspects of clinical nephrology, including patient consultation, outpatient nephrology, hemodialysis, peritoneal dialysis, hemofiltration, vascular access, hypertension, fluid and electrolyte disorders, and renal transplantation. Trainees rotate at The Rhode Island and Miriam hospitals and also see patients in outpatient dialysis facilities. The Division has an extensive didactic program for trainees that includes four to five conferences per week in which the fellows take an active role. Fellows also teach and direct the activities of Brown residents and students taking nephrology electives.

Major areas of research include the progression of renal disease, glomerular hemodynamics, experimental hypertension, diabetic nephropathy, molecular control of renal growth and injury repair, growth factors and receptors, renal effects of diet and antihypertensive agents, molecular determinants of cardiac hypertrophy, cell volume regulation, ion exchange and transport properties along the nephron, and the regulation of intracellular pH. The laboratories are equipped for a wide range of techniques, including whole-animal physiology; ultrasonic blood flow determination; micropuncture; isolated perfused tubule; intracellular ion fluorescence; morphometric image analysis; ELISA; radioimmunoassays, and receptor assays; cell culture; Northern, Southern, and Western analysis; RNase protection assay; PCR; and gel-shift assay. There is also a clinical research program in hypertension and renal disease with a dedicated research clinic and full-time research coordinator. The director of the division is Lance D. Dworkin, MD, and the fellowship program director is J. Gary Abuelo, MD.

Acute Renal Failure and the MELAS Syndrome, a Mitochondrial Encephalomyopathy

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Abstract

MELAS (mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes) is one of a group of heterogeneous yet clinically distinct syndromes ascribed to a defect in mitochondrial function. Here, the case of a patient diagnosed with the MELAS syndrome who subsequently developed acute renal failure is reported. Although no clear renal insult was evident at the time, the clinical picture was consistent with the diagnosis of acute tubular necrosis. The patient’s renal function subsequently returned to baseline. This article reviews the literature concerning renal involvement in the mitochondrial encephalomyopathies, including MELAS, and proposes a mechanism by which patients suffering from mitochondrial disorders may be more susceptible to renal hypoxic injury and acute renal failure.

Key Words: MELAS, acute renal failure, mitochondrial encephalomyopathies

Over the past decade, defects in mitochondrial function have increasingly been associated with human disease. Many of these diseases have now been ascribed to specific mutations in the mitochondrial genome and share a maternal pattern of inheritance. Diseases related to lesions of mitochondrial
DNA (mtDNA) can be divided into two groups: pure encephalopathies with no gross morphological muscle abnormalities, and mitochondrial encephalomyopathies that are associated with ragged-red muscle fibers. The latter group of mitochondrial encephalomyopathies encompasses a diverse group of distinct clinical syndromes with characteristic signs and symptoms. These include myoclonic epilepsy with ragged-red fibers (MERRF), Kearns-Sayre Syndrome (KSS), and mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) (1).

Renal involvement in patients with mitochondrial encephalomyopathies has been demonstrated by clinical symptomatology, biopsy, and molecular genetic studies. In this paper, we report a case of acute nonoliguric renal failure in a patient with the MELAS syndrome. We review the literature concerning renal involvement in patients with biopsy-proven mitochondrial disorders and propose a mechanism by which these patients may be more susceptible to renal failure as a result of their mitochondrial disease.

CASE REPORT

The patient is a 46-yr-old white female admitted to the hospital for an acute deterioration in mental status. Nine months before admission, she had two tonic-clonic seizures. Work-up at that time included a magnetic-resonance imaging study of the brain with gadolinium which showed a nonenhancing right temporal lobe lesion consistent with a cerebrovascular accident. The patient did well until 1 wk before admission, when she developed hallucinations and garbled speech. On the day of admission, she was unable to obey commands or answer questions.

She had a past medical history of type II diabetes mellitus since age 29, and was now insulin-dependent, with peripheral neuropathy and enteropathy. There was a history of cognitive delays, mild mental retardation, cardiac dysrhythmias, and bilateral sensorineural deafness. Her medications included phenytoin and insulin.

On examination, the patient was a thin white woman with short stature. She was alert but would not interact with the examiner. Her blood pressure was 150/90 mm Hg, pulse 96 beats/min, respiratory rate 18 breaths/min, and temperature 99°F. Abnormal findings were limited to the neurological exam. She had increased motor tone throughout and an asymmetric Achilles tendon reflex, 2+ on the right and trace on the left. She moved all four extremities without difficulty and withdrew all four extremities to pain. Laboratory studies on admission included a BUN concentration of 11 mg/dL, creatinine concentration of 0.9 mg/dL, and glucose level of 386 mg/dL.

Further workup included an electroencephalogram that was negative for epileptiform activity. A magnetic resonance imaging study with gadolinium showed a cortical lesion involving the left temporal, parietal, and occipital lobes, with patchy, ill-defined contrast enhancement. This was felt to be consistent with encephalitis. A lumbar puncture revealed clear cerebrospinal fluid with no nucleated cells, no red blood cells, 65 mg/dL of protein, and 153 mg/dL of glucose. Rapid plasma reagin, Lyme, and viral antibody titers were negative. During this time, the patient remained awake, alert, agitated, and vocal but noncommunicative.

The Hospital Course

The patient underwent a brain biopsy of her cortical lesion. A detailed morphologic description of the brain biopsy has been presented elsewhere (E. Stopa, manuscript submitted). Electron microscopy revealed bizarre, enlarged mitochondria with irregular abnormal cristae—findings consistent with but not specific for a mitochondrial disorder (Figure 1). However, molecular analysis of the brain biopsy revealed that 80% of the mitochondria had the typical genetic mutation associated with MELAS. (J. Gilchrist, personal communication; see Discussion). The serum lactate level ranged between 3.1 and 4.8 mEq/L on repeated measurements and a diagnosis of MELAS syndrome (mi-

Figure 1. Ultrastructural findings on brain biopsy. This photomicrograph is remarkable for bizarre, enlarged mitochondria with irregular, abnormal concentric cristae (original magnification, X55,000).
tochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes) was made.

During the next month, the patient underwent an exploratory laparotomy for a suspected perforated viscus, experienced fluctuating glucose values, had intermittent vomiting and poor food intake by mouth (eventually requiring percutaneous endoscopic gastrostomy tube placement for enteral feedings), and developed an *Escherichia coli* urinary tract infection, which was treated with iv ampicillin for 10 days. During this time period, however, her renal function remained stable.

On hospital Day 66, the patient was noted to have a heart rate of 100 bpm, a blood pressure of 92/62 mm Hg, BUN concentration of 37 mg/dL, a creatinine concentration of 1.6 mg/dL and an elevated anion gap of 22 mEq/L (from 13 mEq/L 1 day previously). The patient had a baseline blood pressure of 120/70 mm Hg. She was believed to be volume-depleted and was given iv fluid therapy with normal saline. Despite this treatment, she became oliguric (200 mL urine output over 24 h) and her serum creatinine concentration progressively rose to a value of 4.0 mg/dL after 48 h. Urinalysis showed a specific gravity of 1.005, pH of 6.0, trace protein, and no blood by dipstick, with 0 to 2 red blood cells, 0 to 5 white blood cells, no red blood cell casts, and occasional tubular epithelial cells by microscopic examination. Repeat urinalysis was unchanged. Urine electrolyte studies revealed a urine sodium level of 113 mEq/L, urine chloride level of 99 mEq/L, and urine osmolality of 264 mosmol. The serum osmolality was 293 mosmol.

As the patient’s creatinine level continued to rise, she developed a progressive metabolic acidosis. On hospital Day 69, her BUN concentration was 62 mg/dL, her creatinine concentration was 4.7 mg/dL, and serum CO₂ level was 15 mEq/L, which eventually fell to 11 mEq/L. The serum lactate level was 3.9 mEq/L. Therapy with iv bicarbonate was initiated.

The patient’s serum creatinine concentration peaked at 5.4 mg/dL 4 days after the initial increase was noted, with a BUN concentration of 71 mg/dL. Additional studies revealed a serum eosinophil percentage of 4%, no urine eosinophils, and no skin rash. Subsequently, the patient’s urine output increased to 4.3 L over a 24-h period and then diminished to 1 to 2 L/day. The acidosis improved once renal function returned to normal and bicarbonate therapy was stopped. The patient’s creatinine concentration had fallen to 1.1 mg/dL by the time she was discharged.

**DISCUSSION**

Great heterogeneity exists in the presentation of mitochondrial diseases, but they can be classified into distinct syndromes. Mitochondrial diseases are multisystemic and most commonly affect the brain and the muscle, hence the term encephalomyopathy. Nevertheless, other organs can be affected as well, most commonly the heart, pancreas, and hematopoietic system. The liver, endocrine glands, and kidney are less often affected. Clinical distinctions between three of the major syndromes are listed in Table 1. Diagnosis can now be made at a genetic level as well; an A to G point mutation in the tRNALeu(UUR) gene at nucleotide 3243 has been described in patients with MELAS. Approximately 80% of MELAS patients have been found to have this mutation (3). MELAS mutations can now be detected by molecular analysis of peripheral blood samples (4).

Patients affected by mitochondrial encephalomyopathies have both normal and mutant mitochondrial DNA coexisting in all tissues. This is termed heteroplasmy, and explains how mitochondrial disease can variably affect many organ systems. If a mitochondrial DNA mutation occurs early in development, then mitochondria with mutated genomes will assort randomly among daughter cells during mitosis. In the process of development, different cells acquire varying numbers of mutated and wild-type mtDNA. Cells containing a higher ratio of mutant-to-wild-type mitochondrial genomes will be more likely to show significant clinical dysfunction, particularly in those tissues with high demands for oxidative energy (5).

In addition, it has been proposed that tissues with a high mitotic index, such as hematopoietic cells, are able to select against heteroplasmic cells over the course of many generations of cell division, so that the ratio of mutant to normal mitochondria decreases with age. This explains the spontaneous resolution of anemia seen in patients with long-standing mitochondrial disease (6). On the other hand, in tissues with little mitotic activity, including brain and muscle, the ratio of mutant to normal mitochondria will increase with age, which accounts for the later onset of progressive neuromuscular dysfunction (7). The mechanism for selection favoring mtDNA with deletion is unclear, but might be related to an increased mitochondrial proliferation in response to deficient energy production (8). Ultimately, the clinical involvement of any given organ will depend on at least two factors: the percentage of abnormal mitochondria and the requirement of that organ for functioning mitochondria (i.e., the relative demand on oxidative metabolism) (5). For each individual patient, different organ systems will be affected to varying degrees.

Another interesting feature of these diseases is that both mitochondrial division and mtDNA replication are random processes unconnected to the cell cycle, resulting in mitotic segregation of mtDNA (9). It is for this reason that the proportion of mutant mtDNA can vary both in space (e.g., different tissues) and in time in heteroplasmic patients. As such, patients may each present with entirely different constellations of symptoms over their lifetimes.

Kidney involvement in mitochondrial encephalomyopathies, although infrequent and usually late in the course of disease, has been well-documented. The most commonly observed abnormality is renal tubular dysfunction, which has been associated with a wide
TABLE 1. Mitochondrial encephalomyopathies

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Distinguishing Symptoms</th>
<th>Previous Reports of Renal Involvement (Reference Number)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kearns-Sayre Syndrome (KSS)</td>
<td>Onset before age 20, Ophthalmoplegia, Retinal degeneration, Heart block, CSF protein &gt;100 mg/dl</td>
<td>Chronic renal failure (4), Fanconi’s syndrome (4,5,6), renal Tubular acidosis (7), Bartter’s syndrome (8), Acute nonoliguric renal failure (6)</td>
</tr>
<tr>
<td>Myoclonic Epilepsy with Ragged-red fibers (MERRF)</td>
<td>Myoclonus, Ataxia, Weakness, Seizures</td>
<td>None reported</td>
</tr>
<tr>
<td>Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-like Episodes (MELAS)</td>
<td>Seizures, Repeated stroke-like episodes with neurologic deficits, Hemiparesis, hemianopsia, Cognitive regression, Episodic vomiting, Cortical blindness</td>
<td>Proteinuria (9,10,11)</td>
</tr>
<tr>
<td>Symptoms Common to All</td>
<td>Sensorineural hearing loss, Dementia, Short stature, Weakness, Lactic acidosis, Ragged-red muscle fibers on biopsy, Spongy degeneration of the brain</td>
<td></td>
</tr>
</tbody>
</table>

*Data modified from Reference 1.

A variety of mitochondrial disorders. These include the Kearns-Sayre syndrome (10,11), mitochondrial myopathy (12), and Pearson’s syndrome (13), all of which usually present in early childhood. Occasionally, patients may first present with renal abnormalities, including the de Toni-Fanconi-Debre syndrome (12,13), renal tubular acidosis (10), and defects mimicking Bartter’s syndrome (12). Details of the biopsy-proven renal findings in patients with mitochondrial encephalomyopathies are found in Table 2.

Kidney involvement has also been reported in patients with the MELAS syndrome. Nephrotic-range proteinuria has been noted in three cases (14–16). Postmortem study of one patient revealed global glomerulosclerosis and interstitial fibrosis consistent with an end-stage kidney (14). Biopsy-proven focal glomerulosclerosis was found in the other two patients (15,16). A pedigree study of three generations carrying the MELAS mutation demonstrated heteroplasmic mitochondria in the kidney. Polymerase chain reaction amplification and Southern analysis of DNA retrieved from the kidney of the deceased proband and from the proband’s deceased son revealed 60 to 63% of the mitochondria to be mutant (17). Acute nonoliguric renal failure has been observed in a patient with Kearns-Sayre syndrome, who also had stroke-like episodes as seen in MELAS. Muscle biopsy of this patient, however, did not yield evidence of the MELAS tRNA point mutation (18).

Our patient had the MELAS syndrome and a complex hospitalization complicated by acute renal failure. She developed transient oliguria that was unresponsive to the administration of fluids, and a progressive increase in serum creatinine concentration that peaked after 4 days, followed by a vigorous diuresis. Within 10 days, her creatinine level had almost returned almost to baseline. Her clinical course and laboratory studies are most consistent with a diagnosis of acute tubular necrosis. Notably, no obvious inciting event was identified.

Hypoxic injury results when energy supply and substrate provision are inadequate to serve a tissue’s metabolic demands (19). Although renal blood flow is extremely high, the unique countercurrent anatomical structure of the renal medulla makes it particularly susceptible to ischemic injury. Previous studies have delineated the thick ascending limbs and, to a lesser extent, the S3 portion of the proximal tubules as areas of the medulla in which structural factors limit the availability of oxygen (20). On the other hand, the principal determinant of medullary oxygen requirement is the rate of active reabsorption along the thick ascending limb, and oxygen consumption is, predictably, ten times higher in this region than in the rest of the kidney (21). Thus, the combination of low oxygen delivery and high metabolic rate serves to make the renal tubules unusually susceptible to hypoxic damage. In fact, renal tubular involvement has
TABLE 2. Patients with mitochondrial disorders who underwent renal biopsy

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Renal Symptoms</th>
<th>Renal Biopsy Findings</th>
<th>Ultrastructural Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kearns-Sayre Syndrome (5,7,8)</td>
<td>Renal tubular acidosis, hypocalcemla</td>
<td>Extensive glomerulosclerosis with tubular atrophy; thick-walled vessels with intimal fibrous tissue proliferation and mononuclear infiltrate</td>
<td>Enlarged mitochondria in epithelium of convoluted tubules with abnormal peripherally oriented cristae</td>
</tr>
<tr>
<td>Fanconi's syndrome</td>
<td>Hyaline casts in distal tubules; Interstitial fibrosis and inflammatory cell infiltrate; periglomerular fibrosis</td>
<td></td>
<td>Increased numbers of abnormal mitochondria in proximal and distal tubular cells</td>
</tr>
<tr>
<td>Bartter's syndrome</td>
<td>Not reported</td>
<td></td>
<td>Increased number of mitochondria but no structural changes in proximal tubules; increased numbers of giant mitochondria with abnormal cristae in distal tubules</td>
</tr>
<tr>
<td>Kearns-Sayre/Pearson's Syndrome (4)</td>
<td>Partial Fanconi's syndrome, chronic nonoliguric renal failure</td>
<td>Irregular retraction of the glomerular tuft with dilatation of Bowman's space; stripe-like atrophy of the medullary ray with interstitial fibrosis; PAS-positive fibrillar casts in atrophic tubules, immunofluorescence negative for immunoglobulins or complementa</td>
<td>Increased number of pleomorphic mitochondria with disoriented cristae in proximal tubules</td>
</tr>
<tr>
<td>Pearson's Syndrome (4)</td>
<td>Polyuria, metabolic acidosis, Fanconi's syndrome</td>
<td>Tubular dilatation with degenerative changes in tubular epithelium; Immunofluorescence negative for immunoglobulins, complement, or fibrin</td>
<td>Giant mitochondria in proximal tubules</td>
</tr>
</tbody>
</table>

a PAS, periodic acid-Schiff.

been demonstrated by both pathologic analysis and by molecular genetic studies in mitochondrial encephalomyopathies (6,10,13,22). Pathologic studies have demonstrated dilated tubules in patients with MELAS (14,15) and DNA studies of patients with MELAS have demonstrated the presence of mutated mitochondrial genomes as well (17).

In our case, we presume that the kidneys of our patient were heteroplasmic for mutant mitochondrial genomes. The mild hypotension seen in our patient might not result in an ischemic injury in a healthy host; however, it seems likely that this factor, combined with her mitochondrial disease, was sufficient to produce acute tubular necrosis. A kidney biopsy might have provided more definitive information, but this procedure did not seem clinically indicated for this patient.

Lactic acidosis, commonly seen in patients with mitochondrial encephalomyopathies and also noted in this patient, is a consequence of impairment in oxidative metabolism because of defective mitochondria. During normal metabolism, pyruvate is transported across the mitochondrial membrane into the mitochondrion to undergo oxidative decarboxylation to acetyl coenzyme A (CoA) by pyruvate dehydrogenase (Figure 2). Acetyl CoA is then shuttled into the Krebs cycle, which then contributes electrons to the electron transfer chain. Defects in complex I (NADH coenzyme Q reductase), complex III (reduced coenzyme Q-cytochrome c reductase), and complex IV (cytochrome c oxidase) of the mitochondrial respiratory chain have been documented in patients with MELAS (23).

Because of the impaired utilization of pyruvate in the Krebs cycle, excess NADH accumulates in the cytosol. Under anaerobic conditions, pyruvate is then reduced to lactate by lactate dehydrogenase and one stoichiometric equivalent of ATP is produced. The hydrolysis of ATP yields one equivalent of hydrogen ion, which then must be buffered by extracellular bicarbonate. Bicarbonate is consumed, lactate accumulates, and lactic acidosis develops (24).

In summary, the mitochondrial encephalomyopathies are a diverse group of clinical syndromes that present with multiple organ-system involvement, including the kidney. In some cases, kidney dysfunction can be the predominant symptom and patients with
Acute Renal Failure and the MELAS Syndrome

The NADH/NAD ratio will increase, downregulating PDH. The mitochondrial syndromes may also predispose patients to tubular necrosis and the syndrome of acute renal failure.

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REFERENCES

2. Deleted in proof.