Acute Renal Failure and the MELAS Syndrome, a Mitochondrial Encephalomyopathy¹

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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, ×55,000).](attachment:brain-biopsy.png)
tochondrial myopathy, encephalopathy, lactic acido-
sis, and stroke-like episodes) was made.

During the next month, the patient underwent an
exploratory laparotomy for a suspected perforated
villus, experienced fluctuating glucose values, had
intermittent vomiting and poor food intake by mouth
(eventually requiring percutaneous endoscopic gas-
troscopy 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.
Urine analysis 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 un-
changed. 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 per-
centage 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 mul-
tisystemic and most commonly affect the brain and
the muscle, hence the term encephalomyopathy. Nev-
ertheless, 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. Diagno-
sis can now be made at a genetic level as well; an A to
G point mutation in the tRNA<sub>Leu(UUR)</sub> gene at nucleo-
tide 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 periph-
eral blood samples (4).

Patients affected by mitochondrial encephalo-
myopathies have both normal and mutant mitochon-
drial DNA coexisting in all tissues. This is termed
heteroplasmy, and explains how mitochondrial dis-
éase can variably affect many organ systems. If a
mitochondrial DNA mutation occurs early in develop-
ment, 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 heteroplastic 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 mitochon-
drial 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 pro-
gressive neuromuscular dysfunction (7). The mecha-
nism for selection favoring mtDNA with deletion is
unclear, but might be related to an increased mito-
chondrial 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 require-
ment 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 symp-
toms over their lifetimes.

Kidney involvement in mitochondrial encephalo-
myopathies, 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 tubule 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>Keams-Sayre Syndrome</td>
<td>Renal tubular acidosis, hypocalcemia</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>(5,7,8)</td>
<td></td>
<td>Hyaline casts in distal tubules; interstitial fibrosis and inflammatory cell infiltrate; periglomerular fibrosis</td>
<td>Increased numbers of abnormal mitochondria in proximal and distal tubular cells</td>
</tr>
<tr>
<td>Fanconi's syndrome</td>
<td></td>
<td>Not reported</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>Bartter's syndrome</td>
<td></td>
<td></td>
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</tbody>
</table>

| Keams-Sayre/Pearson's Syndrome (4) | Partial Fanconi's syndrome, chronic nonoliguric renal failure | Irregular retraction of the glomerular tuft with dilatation of Bowman's space; stripes-like atrophy of the medullary ray with interstitial fibrosis; PAS-positive fibrillar casts in atrophic tubules, immunofluorescence negative for immunoglobulins or complement\(^\text{a}\) | Increased number of pleomorphic mitochondria with disoriented cristae in proximal tubules |
| Pearson's Syndrome (4)           | Polyuria, metabolic acidosis, Fanconi's syndrome       | Tubular dilatation with degenerative changes in tubular epithelium; immunofluorescence negative for immunoglobulins, complement, or fibrin | Glant mitochondria in proximal tubules |

\(\text{a}\) 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 mitochondria 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 mitochondrial 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
renal tubular acidosis, Bartter's syndrome, or Fanconi's syndrome have been described. Lactic acidosis may result from mitochondrial dysfunction. Because of the unique susceptibility of the renal medulla to hypoxia, the mitochondrial syndromes may also predispose patients to tubular necrosis and the syndrome of acute renal failure.

ACKNOWLEDGMENTS

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REFERENCES

2. Deleted in proof.
7. Larsson NG, Holme E, Kristiansson B, Oldfors A, Tulin-