An Autopsy Case of Mitochondrial Encephalomyopathy with Lactic Acidosis and Stroke-like Episodes Syndrome with Chronic Renal Failure

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Abstract

A 25-year-old man developed a stroke-like episode. He suffered from renal failure and became dialysis-dependent. His mother was also dialysis-dependent. A3243G point mutation of the mitochondrial tRNA^{leu} gene was detected in both of them. The patient was diagnosed with mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS), and died of a recurrence of stroke-like episodes at the age of 30. Autopsy revealed numerous abnormal mitochondria in the kidneys, but no renal vascular changes. This is the first report of a MELAS case in which the presence of numerous abnormal mitochondria in podocytes and tubules was confirmed by electron microscopy.

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Key words: mitochondrial cytopathy, mtDNA 3243 point mutation, glomerulosclerosis

Introduction

Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) is a heterogeneous yet clinically distinct syndrome ascribed to defects in mitochondrial function (1). Renal involvement associated with mitochondrial encephalomyopathies has been described in clinical symptomatology, biopsy and molecular genetic studies (2–15), but only a few cases with chronic renal failure have been reported, and detailed pathological studies of such cases are scarce.

We report here an autopsy case of MELAS syndrome with chronic renal failure. This case was reported previously as a clinical report of mother-child cases (16). Mitochondrial abnormalities in the kidneys confirmed by electron microscopy are described as well as unique and interesting pathological findings.

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Case Report

Our patient was a 30-year-old Japanese man with a mtDNA mutation. His mother, who suffered from mild hearing loss and renal failure without other neuromuscular symptoms, had become dialysis dependent in her late forties. At the age of 23, the patient suffered from an attack of gouty arthritis and was diagnosed with hyperuricemia and mild renal dysfunction. One year later he noticed auditory impairment. He developed abrupt nausea, and vomiting, severe headache, and confusion at the age of 25. A CT scan showed cerebellar atrophy and a small area of low density in the left temporal lobe. He was admitted to our hospital and five days later he developed right homonymous hemianopsia, sensory aphasia, and sensory inattention, and a new area of low density in the left occipital lobe appeared on CT. Laboratory test results showed that lactate and pyruvate levels and the lactate-to-pyruvate ratio were elevated in both the serum and cerebrospinal fluid. The biopsied muscle showed ragged red fibers and strongly SDH-reactive blood vessels. Gene analysis revealed the presence of A 3243 G point mutation of the mitochondrial tRNA^{leu} gene in the blood leucocytes and muscle, and gene analysis of the patient's mother showed the same point mutation. Serum concentrations of BUN and creatinine were elevated to 46 mg/dl and 2.2 mg/dl, and creatinine clearance was 14.1 ml/min. An abdominal CT scan disclosed atrophy of the left kidney with chronic renal failure. The patient's renal function then deteriorated progressively and at the age of 28 he developed appetite loss, nausea and vomiting. The BUN and creatinine serum concentration levels at the time were 148 mg/dl, and 7.9 mg/dl, so that hemodialysis was initiated. Stroke-like episodes recurred frequently and the patient's mental level deteriorated gradually. At the age of 30, he became comatose while he was undergoing hemodialysis. A CT scan showed severe brain edema and cingulate hernia-

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Figure 1. CT shows severe brain edema and cingulate herniation.

tion (Fig. 1). He then developed left hemiparesis and convulsion of the right face and right limbs, and 5 days later he died of cardiac failure and pulmonary edema. An autopsy was performed two hours after death.

Pathological Findings

Severe brain edema was observed, but no evidence of occlusion or thrombosis of the main cerebral arteries was found. Circumscribed ischemic areas involved the cerebral cortex and both hemispheres in a diffuse manner with the temporal lobes being affected most severely. Cingulate herniation was also observed, and the heart showed left ventricular hypertrophy. Other pathological findings included pulmonary edema and bronchopneumonia, which were the direct causes of death. Semi-thin sections showed microvacuoles in the striated muscles, liver, kidney, and in the cortex and medulla of the adrenals.

The kidneys were atrophic and light microscopy showed remarkably sclerotic glomeruli and atrophic tubules. Some remaining glomeruli featured global glomerulosclerosis and hyalinosis consistent with end-stage kidney. There were no changes due to hyperuricemia, no precipitation of uric acid in the renal tubules, nor any changes in uric acid nephritis. Electron microscopy showed numerous enlarged mitochondria con-

A

B

Figure 2. Electron micrograph of the kidney. Accumulation of the abnormally enlarged mitochondria with complex cristae and paracrystalline inclusions appeared most severely in the podocytes. A. (Magnification, $\times 5,000$) bar=2 μm , B. (Magnification, $\times 25,000$) bar=0.5 μm .

taining complex cristae in all organs, especially in heart, liver, brain and kidneys. In the kidneys the accumulation of the abnormally enlarged mitochondria with complex cristae and paracrystalline inclusions appeared most frequently in the podocytes and the tubules (Fig. 2). However mitochondria in the smooth muscle cells of the arterial capillaries were normal and no vascular changes were observed in the kidneys.

Discussion

Our patient presented with the symptoms of MELAS syndrome associated with chronic renal failure, and A 3243 G point mutation of the mitochondrial tRNA^{leu} gene was detected. The postmortem study revealed end-stage kidney with remarkable sclerotic glomeruli and atrophic tubules, and electron microscopy showed a large number of enlarged mitochondria containing complex cristae in the glomeruli and tubules. Though the patient had suffered from gouty arthritis, no change due to hyperuricemia was found, and also there were no any changes caused by atherosclerosis nor vasculitis. Judging from the absence of other causes of renal involvement, we considered that the global glomerulosclerosis of this case was consistent with renal involvement of MELAS syndrome. The patient's mother, who had hearing loss and the same point mitochondrial mutation, also suffered from renal failure. It is suggested that the etiology of their renal failure was due to the mitochondrial cytopathies.

Renal involvement in patients with MELAS syndrome, although infrequent, has been reported (8–12, 17, 18). Glomerulopathy, including the nephrotic-range proteinuria syndrome was noted, while biopsy-proven focal segmental glomerulosclerosis or global glomerulosclerosis is found in some cases. However, only a few cases with chronic renal failure have been reported (10, 11). The postmortem study of one patient showed global glomerulosclerosis and interstitial fibrosis consistent with end-stage kidney, and the smooth muscle cells of the arterial capillaries in the kidneys were filled with numerous enlarged mitochondria and cristae (8). The report described that such vascular changes might lead to renal hemodynamic insufficiency and might result in glomerulosclerosis. In the present case, however, a large number of abnormal mitochondria was observed in the glomeruli, especially in the podocytes and tubules, while vascular changes were not seen. This suggests non-ischemic damage and the possibility of metabolic renal disorder caused by intrinsic mitochondrial damage. A pedigree study of three generations carrying the MELAS mutation demonstrated heteroplasmic mitochondria in the kidney (9). Polymerase chain reaction amplification and Southern analysis of the DNA retrieved from the kidneys of these MELAS patients revealed that about 60% of the mitochondria were mutant.

Some reports of MELAS syndrome associated with glomerulosclerosis have been reported (7–11, 17–19) and electron microscopy in one report (7) revealed that the smooth muscle cells of the arterial capillaries were filled with increased numbers of enlarged mitochondria and cristae. However, neither of

these reports (7–12, 17–19) confirmed the presence of abnormal mitochondria in the glomeruli or tubules. The present case thus appears to be the first of MELAS with numerous abnormal mitochondria in podocytes and tubules confirmed by electron microscopy.

The renal involvement associated with mitochondrial cytopathies has been well documented, with the most common abnormality being renal tubular dysfunction (2–7, 14). While renal tubular dysfunction is generally associated with a large deletion in mtDNA or rarely with duplication (2–7, 13–15), all the reported cases involving glomerular lesions were associated with the adenine to guanine transition at position 3243 of the mitochondrial tRNA^{leu} gene (7–11, 13, 17–19). The 3243 mutation was originally detected in MELAS syndrome (20), and recently the same mutation has been found in some patients with non-MELAS-associated phenotypes including PEO (progressive external ophthalmoplegia), maternally inherited diabetes mellitus, sensorineural hearing loss, hypertrophic cardiomyopathy, and hereditary glomerulopathy (21–27). Some types of glomerulonephritis, such as focal segmental glomerulosclerosis, should be seen as a phenotypic expression of this mutation. MELAS is a clinically distinct syndrome, but in some pedigree studies a variety of clinical symptoms have been reported in association with the A 3243 G mutation. In the present case, too, the patient showed a typical course of MELAS, but his mother's clinical signs were hearing loss and renal dysfunction without any other neuromuscular symptoms. Although the dominant clinical features of MELAS and those of other syndromes are different, these diseases associated with the A 3243 G mutation show some common ground of neuromuscular disease and renal insufficiency.

We report a case of MELAS syndrome with chronic renal failure, in which the presence of abnormal mitochondria in glomeruli and tubules was demonstrated electron microscopically. Renal complication in MELAS is rare, but it must be a phenotypic expression of the A 3243 G mutation. Further studies are needed to confirm this hypothesis.

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