Aortic Rupture in Mitochondrial Encephalopathy, Lactic Acidosis, and Stroke-Like Episodes

Stacey H. K. Tay, MD; Douglas R. Nordli, Jr, MD; Eduardo Bonilla, MD; Edward Null, MD; Sara Monaco, MD; Michio Hirano, MD; Salvatore DiMauro, MD

Background: Microangiopathy has been well described in the brain and muscle of patients with mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS).

Objective: To describe a patient with the common A3243G/MELAS point mutation who had aortic rupture and whose mother also died of large vessel rupture.

Design: Case report.

Setting: Collaboration between a primary care hospital and 2 academic tertiary care hospitals.

Results: Histologically, there was marked disarray of the smooth muscle architecture of the aorta, and immunohistochemical staining with antibodies against the mitochondrial DNA-encoded cytochrome-C oxidase I subunit showed uniformly decreased immunostaining of the endothelial and smooth muscle cells of the aorta and vasa vasorum. Polymerase chain reaction and restriction fragment length polymorphism analysis showed that the mutation load was 40.5% in blood but 85.3% in the blood vessels.

Conclusions: The severe vasculopathy in this patient is probably directly related to the high mutation load in the blood vessels. Although aortic rupture is an unusual manifestation of MELAS, it is an important potential complication in patients undergoing minor surgical procedures.

Arch Neurol. 2006;63:281-283

MITOCHONDRIAL ANGIOOPATHY has been well described in the brain and muscle of patients with mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS). Previous studies have documented the accumulation of abnormal mitochondria in smooth muscle and endothelial cells of pial arterioles and small cerebral arteries up to 250 µm in diameter1 and in the pericytes of capillaries, smooth muscle, and endothelial cells of small vessels in skeletal muscles.2,3 In addition, abnormal mitochondria have also been described in the vasa nervorum of patients with MELAS and patients with other mitochondrial diseases, such as mitochondrial myopathy, Kearns-Sayre syndrome, and progressive external ophthalmoplegia.4 While small-vessel disease is clearly related to the clinical manifestations of MELAS, such as encephalopathy, stroke-like episodes, and myopathy,5 large-vessel involvement has not been documented previously. We report a patient with MELAS and the A3243G mutation who died of aortic rupture and whose mother died under similar circumstances.

METHODS

PATIENT

This 13-year-old girl was seen in early childhood with learning disability. At 10 years of age, she had recurrent episodes of generalized convulsions in the setting of “heat exhaustion.” She continued to have seizures, predominantly focal in nature, with prolonged hemiparesis following each event. Magnetic resonance imaging of the brain demonstrated multiple areas of increased signal abnormalities in the cortex, particularly in the posterior cortex. These signal abnormalities appeared and disappeared over the years, shifting in location without apparent cystic transformation or evolution to encephalomalacia. The patient underwent genetic testing and was found to harbor the A3243G/MELAS mutation.

At 15 years of age, during gastrostomy insertion, she had spontaneous rupture of the thoracic aorta. During an unsuccessful attempt to repair the rupture, it was noted that the aorta was extremely friable. At autopsy, the aorta showed an intact intima without atherosclerotic changes. Microscopic examination showed a rupture, and the adjacent wall showed disorganized smooth muscle layers and disrupted elastic layers. The patient’s mother had died several years earlier of a major vessel rupture during angiography.
METHODS

Histopathologic Studies

Paraffin-embedded sections of the aorta were stained with Gomori trichrome stain. Immunohistochemical staining with antibodies against cytochrome-C oxidase (COX)I (representative of mitochondrial DNA-encoded proteins) and COX IV (representative of nuclear DNA-encoded proteins) was performed as previously described.6

Molecular Analysis

Total DNA was extracted from blood and paraffin-embedded slices of the aorta using the Puregene DNA Purification Kit (Gentra Systems, Minneapolis, Minn) according to the manufacturer’s protocol. Aortic tissue was deparaffinized using xylene. Polymerase chain reaction amplification of mitochondrial DNA was performed using oligonucleotide primers corresponding to nucleotide positions 3116 to 3134 (forward) and 3353 to 3333 (reverse). Quantitation of the A3243G mutation load was performed as previously described.7

RESULTS

There was marked disruption of the smooth muscle and elastic layers of the aorta, which were evident adjacent to the rupture site but also in the rest of the intact aortic wall (Figure 1). Immunohistochemical studies showed that COX I staining of the smooth muscle cells was much less intense than COX IV staining (Figure 2), implying a lesser production of mitochondrial DNA-encoded proteins (COX I) than of nuclear DNA-encoded proteins (COX IV). Decreased COX I staining was also present in the vasa vasorum of the aorta. There was no evidence of aneurysmal dilatation of any large vessels (data not shown).

Quantitation of A3243G mutant genomes in blood showed a mutation load of 40.5%. The mutation load was much higher in 2 large aortic vessels, where it ranged from 83.3% to 87.3% (mean, 85.3%) (Figure 3). No other tissues were available for analysis.

COMMENT

To our knowledge, this is the first report of large-vessel involvement in MELAS, which resulted in catastrophic aortic rupture after a trivial surgical procedure. There is a strong possibility that the patient’s mother, who was an obligatory carrier of the A3243G mutation and died of a ruptured vessel, also had large-vessel disease.

Figure 1. Morphology of a cross-section of the ruptured aorta with Gomori trichrome staining under low magnification (A) and of the circled area seen at higher magnification (B). There was marked disruption of the smooth muscle and elastic layers of the tunica media.

Figure 2. Immunohistochemical staining for cytochrome-C oxidase (COX) I at lower (A) and higher (D) magnification and for COX IV at lower (B) and higher (D) magnification. There was decreased COX I but normal COX IV staining of the smooth muscle cells in the media and of the endothelial cells of the vasa vasorum in the adventitial layer.
Histopathologic examination of the patient’s aorta demonstrated disruption of the smooth muscle layers. This may be directly attributable to mitochondrial dysfunction and decreased production of mitochondrial DNA-encoded proteins due to the underlying transfer RNA<sup>1</sup>eu(UUR) defect. In fact, we documented a high A3243G mutation load of about 85% in the aorta, suggestive of severe mitochondrial dysfunction in this tissue. Alternatively, because the COX I staining was also decreased in the vasa vasorum of the aorta, the abnormalities of the smooth muscle layers could have been caused by impaired blood supply to large vessels by the affected vasa vasorum.

Although the patient had high mutation loads both in large vessel walls and in blood (Shanske et al. reported a mean ± SD mutation load of 23.47 ± 19.6 in the blood of patients with symptomatic MELAS), the A3243G mutation loads in easily accessible tissues, such as urine sediment and blood, do not correlate well with the mutation loads in less accessible tissues, such as brain and skeletal muscle. Therefore, it is impossible to predict the mutation load in blood vessels in patients with MELAS and the attending risk of large-vessel disease. A recent study by Takahashi et al. described abnormal capacitive and oscillatory compliance on pulse wave analysis in a single adult patient with MELAS. Their patient and ours may represent the extreme spectrum of vascular involvement, but further studies are needed to establish the frequency and severity of large-vessel disease in patients with MELAS.

While large-vessel vasculopathy is a rare finding in MELAS, precautions should be taken before embarking on both trivial and major surgical procedures. Systemic vascular assessment may be prudent in these patients.

Accepted for Publication: July 25, 2005.
Correspondence: Salvatore DiMauro, MD, 4-420 College of Physicians and Surgeons, 630 W 168th St, New York, NY 10032 (sd12@columbia.edu).

Author Contributions: Study concept and design: Tay, Bonilla, Hirano, and DiMauro. Acquisition of data: Tay, Nordli, Bonilla, Null, and Monaco. Analysis and interpretation of data: Tay, Bonilla, Hirano, and DiMauro. Drafting of the manuscript: Tay, Nordli, Monaco, Hirano, and DiMauro. Critical revision of the manuscript for important intellectual content: Bonilla, Null, and Hirano. Administrative, technical, and material support: Tay, Bonilla, Null, Monaco, Hirano, and DiMauro. Study supervision: Tay, Bonilla, and DiMauro.

Funding/Support: This study was supported by grant HD32062 from the National Institutes of Health, Bethesda, Md; a grant from the Muscular Dystrophy Association, Tucson, Ariz; and the Marriott Mitochondrial Disorders Research Fund, Chevy Chase, Md. Dr Tay was supported by the National Medical Research Council Medical Research Fellowship, Singapore.

Clinical Research Fund, Chevy Chase, Md. Dr Tay was supported by the National Medical Registration Council Medical Research Fellowship, Singapore.

REFERENCES