Evolution of Cardiac Involvement in Progressive Ophthalmoplegia with Deleted Mitochondrial DNA

Paola Melacini, M.D., Corrado Angelini, M.D.,* Gianfranco Buja, M.D., Gianfranco Micaglio, M.D.,* and Maria Luisa Valente, M.D.**

SUMMARY
A 43-year-old woman with progressive external ophthalmoplegia developed a bifascicular block and dilatation of the right ventricle during 4 years of follow-up. Histochemical and electron microscopy studies detected mitochondrial abnormalities in ocular, skeletal muscle and cardiac biopsies. This case registers disease progression from the external ocular to the skeletal and cardiac muscles. Mitochondrial DNA was deleted in relation to the morphological abnormality.

Additional Indexing Words:
External ophthalmoplegia Cardiac biopsy

PROGRESSIVE external ophthalmoplegia, a mitochondrial myopathy,1) is often associated with either cardiac conduction defects2)–6) or congestive heart failure.6) We describe a patient with ophthalmoplegia in whom electrophysiologic study and right endomyocardial biopsy were performed. Ultrastructural and histochemical changes in ocular, skeletal and cardiac muscles are compared.

CASE REPORT
At the age of 30 years, the woman developed progressive bilateral ptosis and required corrective surgery 1 year later. At 39 years of age, she was admitted to the Neurologic Clinic, where examination revealed ptosis, bilateral pigmentary retinopathy, and restricted extraocular movements in all directions; CPK and aldolase levels were 814 and 9.3 U/L, respectively (normal values, 0–145 and 1–7.7 U/L, respectively). At this time, a first muscle

*From the Departments of Cardiology, *Neurology and **Pathology, University of Padua Medical School, Padua, Italy.
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Address for reprints: Paola Melacini, M.D., Department of Cardiology, Via Guistiniani, 2, 35100 Padua, Italy.
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biopsy (triceps) showed only type I atrophy, a nonspecific feature.

Contemporaneous biopsy of the levator palpebræ revealed that the ocular myofibers contained many large subsarcolemmal mitochondria with concentrically arranged cristae (Fig. 1A), near lipid droplets and glycogen granules. Her first electrocardiogram recorded at age 39 disclosed a left posterior fascicular block (Fig. 2A), while results of clinical examination, chest x-ray and echocardiogram were normal. At the age of 42, she was again admitted to
the Neurologic Clinic for evaluation of dyspnea. Respiratory tests showed a restrictive pattern; amplitude of the evoked brain stem potentials was reduced. A routine electrocardiogram displayed different degrees of incomplete right bundle branch block associated with a posterior fascicular block.

A second muscle biopsy (biceps) exhibited the typical ragged-red fibers on trichrome stain, many subsarcolemmal mitochondria, prevalence of type I fibers, and scattered lipid droplets. Biochemical determination of skeletal muscle mitochondrial enzymes revealed a 22% reduction in cytochrome C oxidase (1.74 um/min/gww; control mean: 2.23). Serum carnitine was nor-
Basal lactate level was 16.6 mg/100 ml (normal range: 3.5–22.5 mg/100 ml); however exertional lactic acidosis was detected 5 min after a 15 min cycling effort, as lactic acid levels rose to 74 mg/100 ml (control: 22±16 mg/100 ml). At 43 years of age, the patient was admitted to the Cardiology Department because of dizziness. On this occasion, an electrocardiogram demonstrated persistent complete right bundle branch block and posterior fascicular block (Fig. 2B). Two-dimensional echocardiogram disclosed a normal left ventricle and a dilated right ventricle; the normalized end-diastolic volume, calculated by the area-length method, and the ejection fraction were 93 ml/m² and 49%, respectively (Fig. 3). Pulsed Doppler revealed a mild tricuspid regurgitation.

Electrophysiologic study showed normal atrioventricular conduction times (PA=20 ms, AH=70 ms, HV=50 ms, Wenckebach point=200 bpm), and sinus node function (maximal corrected sinus node recovery time=400 ms, sino-atrial conduction time by the Narula method=200 ms). The ventricular extrastimulus technique during ventricular drive pacing of 600–500 ms initiated only isolated ventricular responses. At the end of the electrophysiological investigation, pressures in the right atrium and ventricle were normal. A right ventricular endomyocardial biopsy was performed at the level of the interventricular septum. The myocardial tissue showed a normal structure in routinely stained sections. Myocardial cells, however exhibited a wide variety of ultrastructural alterations; large areas of disarray and lysis of myofilaments were present (Fig. 1B), and subsarcolemmal clusters of mitochondria with electron-dense matrices and tubular cristae were frequent.

* Analysis of a muscle fragment (courtesy of Dr. DiMauro, Columbia University, New York) showed that mitochondrial DNA was deleted in our patient.
DISCUSSION

A definite nosological difference between the Kearns-Sayre syndrome (KSS) and ophthalmoplegia plus is difficult since a younger age at onset is ascribed to the former; in fact, KSS patients show the presence of ophthalmoplegia, heart block and other clinical signs (short stature, pigmentary retinopathy) before the age of 20.\textsuperscript{1,7} Recently, Holt et al\textsuperscript{8} and Zeviani et al\textsuperscript{7} described mitochondrial DNA deletion in both KSS and ophthalmoplegia plus. This genetic mitochondrial DNA abnormality, therefore, may be present in both clinical pictures, even though it is more frequently found in KSS. Our patient presented a clinically late onset, with deletion of mitochondrial DNA. In progressive external ophthalmoplegia and in KSS, the conduction system is preferentially affected.\textsuperscript{2}-\textsuperscript{5} Gallastegui et al\textsuperscript{6} reported degenerative myocardial changes with fatty infiltration of the right ventricle and fibrosis of the left ventricle in patients with KSS. In our patient, we observed a progressive impairment of the conduction system with the initial appearance of a left posterior fascicular block, and subsequently a bifascicular block in the absence of intranodal and infrahisian disturbances. These findings point to a peripheral involvement of the Purkinje network; development of the complete and persistent right bundle branch block was correlated with the right ventricle dilatation. Ultrastructural study of the myocardium revealed proliferation of the mitochondria with an abnormal arrangement of cristae suggesting an initial metabolic abnormality of the cardiac cells without evident necrosis. In mitochondrial cardiomyopathies, energy production defects may originate from a mitochondrial deficit and low ATP production per fiber. This in turn may lead to myocardial dilatation when the work load exceeds the energy generated.

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