Myocardial Ultrastructure and the Development of Atrioventricular Block in Kearns-Sayre Syndrome

RICHARD CHARLES, B.SC., M.B., S. HOLT, M.B., J. M. KAY, M.D.,
E. J. EPSTEIN, M.D., AND J. RUSSELL REES, M.D.

SUMMARY A right ventricular endomyocardial biopsy specimen from a 30-year-old male with chronic progressive external ophthalmoplegia, retinal pigmentation and complete atrioventricular block (Kearns-Sayre syndrome) was examined in the electron microscope. There was a proliferation of mitochondria between the myofibrils and beneath the sarcolemma. Many of the mitochondria showed morphologic abnormalities not previously described in this condition. There were associated accumulations of glycogen. A similarly affected female with left anterior hemiblock developed complete atrioventricular block at age 26 years. Despite the ultrastructural changes, clinically detectable myocardial disease is not a feature of Kearns-Sayre syndrome. However, intraventricular conduction defects show an unusually rapid progression to potentially fatal complete atrioventricular block and are an indication for prophylactic cardiac pacing.

CHRONIC progressive external ophthalmoplegia (CPEO), first described by von Graefe in 1868,1 is a myopathic condition of insidious onset and progress that may be associated with a normal life expectancy.2 It may be linked with a wide variety of features, including weakness of the facial, pharyngeal and peripheral muscles, cerebellar ataxia, deafness, small stature, pigmentary degeneration of the retina, abnormal electroencephalographic findings and increased protein content of the cerebrospinal fluid. Drachman3 reviewed the clinical syndromes associated with CPEO, but the pathophysiologic relationships between syndromes including CPEO are obscure. Although some clinical descriptions suggest cardiac involvement in CPEO, the first confirmed report is that of Sandifer,4 whose patient had histologically proved ocular myopathy, an apical systolic murmur and an ECG that showed an irregular bradycardia as low as 20 beats/min, absence of P waves and QRS prolongation. In 1958 Kearns and Sayre5 described two cases of the syndrome that bears their name, which is characterized by CPEO, atypical retinitis pigmentosa and atrioventricular (AV) block. Kearns6 later reviewed the condition and described nine cases, including pathologic examination of the heart at autopsy in one patient. These and subsequent case reports show that cardiac conduction defects may precede the development of potentially fatal complete AV block in young patients. The pathologic nature of the cardiac condition is unclear and the few reports of examination by gross inspection or light microscopy show no specific abnormality. However, electron microscopy of a myocardial biopsy specimen in a single case reported recently7 revealed increased numbers of structurally normal mitochondria.

In this paper we report two additional cases of the Kearns-Sayre syndrome and describe ultrastructural abnormalities of the myocardium not previously observed in this condition. The development of complete AV block in such patients may be preceded by a variable period, during which lesser degrees of conduction disturbance may be manifest.

Case Report

Patient 1

A 26-year-old woman was admitted to hospital after suddenly losing consciousness at home. A squint had been present from birth and glasses were required at 4 years of age. Progressive bilateral ptosis developed at age 10 years, and required corrective surgery 4 years later when all ocular movements were found to be restricted. Progressive deafness commenced at 11 years of age. She had no evidence of neurologic disease in her parents or two brothers, who also had normal ECGs. A paternal cousin had dystonia musculorum deformans and two uncles had strabismus. Neurologic examination at age 19 years revealed bilateral ptosis, partial external ophthalmoplegia and bilateral nerve deafness. The right ocular fundus was obscured by keratitis, but there was a pale disc on the left with fine scattered pigmentation at the periphery of the retina. Pupil reactions were normal, as were the remaining cranial nerves. The neck and limb muscles were unaffected and sensory modalities were unimpaired. She had mild ataxia of the trunk and limbs, which was worse on the left. The blood pressure was 125/90 mm Hg and the cardiovascular examination was normal. The ECG (fig. 1) showed left anterior hemiblock. The cerebrospinal fluid protein level was elevated to 130 mg/100 ml. The blood count was normal and serologic tests for syphilis were negative. The concentrations of urea, electrolytes, cholesterol and thyroxine in the blood were normal. Chest radiography, air encephalography and the cerebrospinal fluid phytic

From the Regional Cardiac Centre, Sefton General Hospital and the Department of Pathology, University of Liverpool, Liverpool; and the Cardiac Department, Bristol Royal Infirmary, Bristol, England.

Dr. Kay’s present address: Department of Pathology, McMaster University, Hamilton, Ontario, Canada.

Address for correspondence: Dr. E. J. Epstein, Regional Cardiac Centre, Sefton General Hospital, Liverpool L15 2HE, England.

Received January 3, 1980; revision accepted May 15, 1980.

Circulation 63, No. 1, 1981.
acid were unremarkable. On admission, she showed severe bilateral ptosis (fig. 2), almost total external ophthalmoplegia and a high pitched nasal voice. The ECG now showed complete AV block with a ventricular pacemaker (fig. 3). A permanent pacemaker (CPI Minilith) was implanted and no further syncopal episodes have occurred during the subsequent 6 years.

**Patient 2**

A 30-year-old man was admitted to hospital because of a syncopal attack. He had suffered a similar episode at age 10 years and from dizzy spells during the 3 weeks before admission. He had never complained of visual defects, although his parents stated that his eyelids had drooped since early childhood. He was 164 cm tall and weighed 51 kg. He had bilateral ptosis (fig. 4) and severe external ophthalmoplegia with a left divergent squint. Scattered retinal pigmentation was present bilaterally. There was mild bilateral nerve deafness. His heart rate was 40 beats/min, blood pressure 110/50 mm Hg and cannon waves were present in the jugular venous pulse. There was an ejection click and a midsystolic murmur in the second right and left intercostal spaces. The ECG showed complete AV block with a ven-

**Figure 1.** Patient 1 — ECG showing left anterior hemiblock; the mean frontal plane QRS axis is $-45^\circ$. Patient is 19 years old.

**Figure 2.** Patient 1, age 26 years, with severe bilateral ptosis.
tricular pacemaker (fig. 5). The electroencephalo-
gram revealed bilateral slowing of the alpha rhythm
and bilateral theta excess which was paroxysmal.
The blood count was normal and serologic tests for
syphilis were negative. The levels of urea, electrolytes,
B12, folate and creatine kinase in the blood were
normal. Cardiac catheterization showed normal in-
tracardiac pressures and an endomyocardial biopsy
was obtained from the right ventricle. A permanent
pacemaker (Tellectronics 120) was inserted. Three
years later syncope had not recurred and neurologic
disability had not progressed.

Pathology

Methods

The endomyocardial biopsy specimen was divided
into two portions. The first portion of tissue was fixed
in buffered neutral formalin, routinely processed and
embedded in paraffin wax. Sections 5 μ thick were
stained for light microscopy with hematoxylin-eosin;
hematoxylin-Van Gieson; elastic-Van Gieson; or
congo red. The second portion was diced into 1-mm²
blocks and fixed in ice-cold glutaraldehyde for elec-
tron microscopy. This tissue was subsequently post-
fixed in osmium tetroxide, stained with uranyl acetate,
and embedded in araldite. Thin (1 μ) sections were cut
and stained with toluidine blue for examination with
the light microscope and selection of suitable areas of
electron microscopy. Selected ultrathin sections were
stained with lead citrate, mounted on copper grids,
and examined in an AEI EM6B electron microscope.

Light Microscopy

There was fibroelastic thickening of the subendocar-
dial zone that was 27–114 μ wide (normal range up to
20 μ). The muscle cells were hypertrophied and up to
30 μ wide (normal range 5–12 μ) and sometimes con-
tained nuclei that were enlarged, rectangular, and
hyperchromatic. There were no perinuclear haloes or
areas of muscle cell branching and no evidence of
amyloid disease.
Electron Microscopy

The myofibrils were arranged in parallel arrays that showed focal areas of separation caused by a proliferation of mitochondria (fig. 6). In addition to this interfibrillar mitochondriasis, there were also collections of mitochondria beneath the sarcolemma and adjacent to the nucleus, causing it to become elongated, curved and thin. The subsarcolemmal mitochondriasis was not associated with the formation of cardiac villi. Many of the mitochondria showed morphologic abnormalities. Some were swollen, with wide separation and kinking or curving of their cristae. Occasional giant mitochondria were seen (fig. 7). Sometimes these were oval or spherical with numerous long, parallel closely-packed, narrow cristae. Enlarged, bilobed mitochondria shaped like an asymmetrical dumb-bell were also present (fig. 8). These contained widely spaced curved cristae. The proliferated mitochondria showed no evidence of calcification but were frequently associated with accumulations of glycogen in the β-monoparticulate form. Occasional small collections of lipofuscin were seen and there was focal dilatation of the sarcoplasmic reticulum. Only a few intercalated discs were present in the sections examined and they were unremarkable.

Discussion

CPEO occurs alone or as a component of a dozen or more syndromes that affect skeletal muscle, the central nervous system and heart. Such syndromes may be familial or apparently sporadic, as in the Kearns-Sayre syndrome. The wide variety of conditions associated with CPEO has led to uncertainty about the nature of the condition. It is not clear whether the combinations of abnormalities represent separate disease processes or whether they should be regarded as diverse manifestations of a single metabolic defect. There is similar uncertainty about the nature of the cardiac involvement, although the disease has been termed a cardiomyopathy. Jager et al. reported no histologic changes in the heart of a 14-year-old boy with CPEO and AV block who died during a syncopal attack. However, Kearns described left ventricular hypertrophy, enlarged hyperchromatic muscle nuclei and slight endocardial thickening at
In 1973, Morgan-Hughes and Mair described histologic, histochemical and ultrastructural changes in the triceps muscle of four patients with CPEO who had normal ECGs. Their patients had a proliferation of mitochondria, particularly under the plasma membrane and around the nuclei. The mitochondria showed striking ultrastructural changes. Sometimes they were much larger than normal, and clear ballooned spaces occurred between their cristae. A prominent change was the presence of laminated crystalline inclusions lying within the cristae. Considerable deposits of glycogen granules occurred in association with the mitochondria and between the myofibrils. Similar changes had been reported in various other types of myopathy. Proliferation of muscle mitochondria with the formation of paracrystalline crystals was believed to represent a non-specific reaction to a variety of metabolic defects. Similar changes were reported in the triceps muscle of a 32-year-old man with CPEO, pigmentary degeneration of the retina and AV block. Biopsy specimens from the right and left ventricles were examined. Light microscopy showed interstitial fibrosis, hypertrophy of myocardial fibres and thickening of the endocardium. Electron microscopy showed a proliferation of mitochondria that were morphologically normal. The changes were said to be indistinguishable from those of ordinary hypertrophy. Intracardiac pressures were normal. There were no valvular abnormalities that might give rise to cardiac hypertrophy. In our patient 2, there was a proliferation of mitochondria that showed morphologic abnormalities associated with accumulations of glycogen. However, no intramitochondrial crystalline inclusions were seen, so the cardiac muscle changes differed from the skeletal muscle changes reported in CPEO.

Cardiac involvement in neuromuscular disease includes abnormalities of both myocardial and specialized conducting tissue, either of which may be preferentially affected. In Friedreich's ataxia and progressive muscular dystrophy, myocardial involvement may result in death due to congestive cardiac failure. Despite the presence of ultrastructural changes in the myocardium, the lack of clinical heart disease other than conduction defects, with normal intracardiac pressures in our patient 2 and in other case reports, suggests that the metabolic abnormality in Kearns-Sayre syndrome preferentially affects conducting tissue. Furthermore, the progression of intraventricular conduction defects to complete AV block in Kearns-Sayre syndrome appears to be more frequent than in patients with similar defects of other etiology. In a population study, 41% of 248 participants with left-axis deviation had no clinical evidence of heart disease and had no excess incidence of heart disease morbidity or mortality during an average observation period of 4 years. In patients with combined left-axis deviation and right bundle branch block, the risk of progression to complete AV block is 6% per year of follow-up or less. Neither left-axis deviation nor bifascicular block are generally considered to be sufficient indications for prophylactic permanent pacing. Intraventricular blocks in Kearns-Sayre syndrome have a different natural history. Patients with combined left anterior hemiblock and
right bundle branch block,\textsuperscript{3, 18, 22} right bundle branch block alone\textsuperscript{6} and left bundle branch block\textsuperscript{9} have progressed to complete AV block during the second decade of life. Kearns' case 6, a 13-year-old boy, had left-axis deviation but progression to complete AV block was not recorded.\textsuperscript{6} In our patient 1, isolated left anterior hemiblock progressed to complete AV block by age 26 years. Thus, in contrast with sclerodegenerative disease, fascicular blocks in Kearns-Sayre syndrome carry a high risk of early and potentially fatal progression to complete AV block, and prophylactic permanent pacing should be considered. In view of the associated abnormalities of myocardial ultrastructure, prolonged survival in paced patients could allow the emergence of a clinically overt cardiomyopathy in this condition.

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R Charles, S Holt, J M Kay, E J Epstein and J R Rees

doi: 10.1161/01.CIR.63.1.214

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