The Heritable Syndrome of Prolonged Q-T Interval, Syncope, and Sudden Death*

Electron Microscopic Observations

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A family with the heritable syndrome of prolonged Q-T interval is reported. Three members died suddenly. Six had a prolonged Q-T interval. One had syncopal episodes for four years but has had no syncope since therapy with propranolol was initiated two years ago. The inheritance appears to be autosomal dominant. There was no evidence of hearing defects. Histologic and electron microscopic studies were performed on cardiac tissue from one patient. This is the first report of electron microscopic studies, and the findings suggest a possible defect of calcium metabolism in the myofiber.

The heritable syndrome of deafness, prolonged Q-T interval, syncopal episodes, and sudden death was described in 1957. A similar syndrome without hearing defects but with an autosomal dominant, rather than recessive, inheritance was described in 1963. Three reviews have summarized the cases in the literature. This would appear to be an uncommon syndrome; however, it may be more often unrecognized than rare. The etiology of the cardiovascular abnormalities has been elusive. This is the first report of electron microscopic studies, and they are suggestive of a congenital myocardial metabolic disturbance of calcium as the underlying defect.

CASE REPORTS

This family (Fig 1) came to our attention in 1973 when one member, a 13-year-old student, was referred because of syncopal episodes with exercise over the preceding four years. His 15-year-old brother had recently died suddenly during a wrestling match and had a history of syncopal episodes for five years. A ten-year-old sister had also died suddenly while exercising. None had evidence of hearing defects.

The heart of the 15-year-old deceased brother was obtained for the pathologic studies discussed herein. An electrocardiogram obtained when this brother was ten years old (Fig 2) showed a prolonged Q-T interval and abnormal T waves.

A clinical evaluation, including a treadmill test and cardiac catheterization, was performed on the 13-year-old student. Findings from physical examination, cardiac catheterization, and angiographic studies were normal. His ECG showed a prolonged Q-T interval. The treadmill test revealed abnormal T-wave changes and a Q-T interval that initially increased and then decreased. The P wave became superimposed on the T wave as the maximal heart rate was reached. The patient had no syncopal episodes while hospitalized. Electrolyte levels including the serum calcium and blood urea nitrogen levels, and a complete blood cell count were normal. The patient was discharged on a regimen of propranolol therapy and has had no syncopal episodes during the past two years.

Pathologic studies

The body of the 15-year-old brother was arterially embalmed one hour and forty-two minutes after death. Eleven hours later, the autopsy was performed, and the heart was fixed in a buffered formaldehyde solution (10 percent Formalin). Findings from gross examination of the 285-gm heart, including the epicardium, coronary arteries, chambers, valves, endocardium, and myocardium, were normal.

The findings from histologic examination of the conduction tissue showed no abnormalities. Electron microscopy revealed disruption, thinning, and disarray of myofibrils, and a decrease in the number of mitochondria. The findings are suggestive of a congenital myocardial metabolic disturbance of calcium as the underlying defect.

Figure 1. Heredity chart for family reported. Three members died suddenly, two have had syncopal episodes, and six have prolonged Q-T intervals. Q-T interval is stated below the age of each member.

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FIGURE 2. Electrocardiogram from 15-year-old obtained when he was ten years old, showing prolongation of Q-T interval (0.51 msec) and T-wave abnormalities. He died suddenly at age 15 years.

FIGURE 3. Myocardium in contracted stage. Number of mitochondria is increased, and nearly all mitochondria contain large rounded granules and linear densities of cristae (original magnification $\times 10,650$).

FIGURE 4. Mitochondrion showing two large rounded granules (original magnification $\times 132,500$).

and its blood supply, including the sinoatrial node, atrioventricular node, His bundle, and bundle branches, were normal using the methods of Hudson,7 and Lev et al.8 Calcium staining tests9,10 were used on multiple sections of the myocardium and gave negative results. Occasional focal areas of myocardium consisted of small groups of swollen myofibers with decreased perinuclear sarcoplasm and lucent zones. Staining tests for glycogen were negative.

Multiple sections of tissue refixed in glutaraldehyde and osmium tetroxide and embedded in Eponsil were examined with an electron microscope (Phillips 200). Although there was a loss of quality in ultrastructural detail due to suboptimal timing of fixation and to initial fixation in the formaldehyde solution, it was our opinion that the findings, nevertheless, were significant and should be described.

Myofibers had uniformly shortened sarcomeres. Mitochondria appeared to be increased in number. The mitochondria frequently were spherical rather than having the usual elongated or oval configuration. Abnormal electron-dense material in two different configurations was seen (Fig 3). Many of the mitochondria contained one or more dense rounded masses between 250 and 300 Angstroms in diameter (Fig 4). The central portions of these granules were the most dense, and the borders were indefinite and fuzzy appearing. The majority of the granules were located just inside the outer membrane; however, some granules were located more in the interior of the mitochondria. The cristae were frequently marked by electron-dense linear areas involving the cristae. Not all mitochondria contained the rounded masses or dense linear changes of the cristae; however, some contained both types of electron-dense changes. Less commonly, stretches of the outer membrane of the mitochondria showed an increased electron-dense appearance.

**Discussion**

**Pathologic Findings**

Pathologic studies have been reported in five cases of prolongation of the Q-T interval and sudden death.11-13 Four of these cases were associated with deafness.11-12 In one case, no deafness was present.13 In the four cases associated with deafness, two cases demonstrated cardiac pathologic findings, and two did not.12 The cardiac specimen in one of these cases, a 14-year-old girl, showed no gross pathologic changes. In the other case, a specimen from a 3½-year-old boy exhibited endocardial fibroelastosis. The histopathologic findings in both cases showed thickening of the intranodal portion of the artery to the sinoatrial node due to hypertrophy of smooth muscle. Hemorrhage was also present in some of the connections of the sinoatrial node to the atrial myocardium, and hemorrhage was present in the nearby parasympathetic ganglia. In one case, hemorrhage was present in ganglia near the atrioventricular node. The specimen from the case in which deafness was absent, an 18-year-old man, demonstrated no gross changes; however, the histologic examination showed two areas of sclerosis and degeneration in the atrioventricular bundle. Stenosis of the superior ventricular septal artery and of the arterioles within the main bundle were also noted.13

Grossly, the heart of the 15-year-old boy in this study was not remarkable. Microscopically, subtle vacuolations were found in occasional myofibers.
The conduction system and the blood supply to the conduction system were intact. The rounded dense bodies observed in the mitochondria by electron microscopic examination resemble the calcium accumulations in mitochondria observed by Shen and Jennings\textsuperscript{14} in experimentally produced myocardial ischemia. The intramitochondrial bodies in this case also resemble the granules noted by Greenawalt et al\textsuperscript{15} in experimentally produced calcium accumulation in hepatic mitochondria of rats. Assuming that the intramitochondrial bodies represent excess accumulation of calcium salts, questions are provoked regarding the abnormal effect of such calcium accumulation on metabolic, electrical, and contractile mechanisms of the myofibers that might lead to abnormal repolarization of the myocardium and fatal ventricular arrhythmias. Although we have not found similar granules using the same technique of preparation in other hearts, the significance of these findings are contingent upon proper controls.

**Clinical Findings**

Since Jervell and Lange-Nielsen\textsuperscript{1} described the syndrome with deafness and an autosomal recessive inheritance in 1957 and since studies by Romano et al\textsuperscript{2} and by Ward\textsuperscript{3} described a similar syndrome without deafness and an autosomal dominant inheritance, there have been several reports of both syndromes.\textsuperscript{4,5,9,16-19} The family in this report qualifies for the syndrome described by Romano and Ward\textsuperscript{3} because of (1) several members with prolonged Q-T intervals, (2) known episodes of syncope in two members, (3) sudden death in three members, (4) autosomal dominant type of inheritance, and (5) absence of hearing defects.

The patients suffering from this syndrome are usually healthy and normal except for episodes which may take three forms: (1) transient episodes of palpitation, numbness, or anginal type of chest pain without loss of consciousness; (2) sudden loss of consciousness usually associated with exertion or emotional stress; and (3) sudden death. This is predominantly a childhood illness with onset usually by the age of three years; however, onset at the age of 30 years\textsuperscript{20} (without deafness) and the age of 61 years\textsuperscript{21} (with deafness) have been reported. In general, the later the onset, the milder the disease; and the threat of sudden death diminishes in adulthood.

The ECG allows definitive diagnosis in the symptomatic patient. Basically, there is an abnormality in electrical repolarization demonstrated by the prolonged Q-T interval and the abnormal configuration of T waves; however, these changes may vary daily in the same patient. When the ECG is normal, exercise may reveal the abnormalities. As a patient grows older, the prolongation of the Q-T interval may normalize,\textsuperscript{20} thus making it difficult to be sure of the number of affected family members. Although electrical systole is prolonged, it has been found that mechanical systole measured by the time between the first and second heart sounds is normal.\textsuperscript{2,22}

The syndrome is inherited, and it seems clear that it is an autosomal dominant inheritance in those patients without evidence of deafness, as illustrated in this family. When congenital hearing loss is associated with the syndrome, the pattern of inheritance is thought to be an autosomal recessive, although there is some suggestion that it could be dominant.\textsuperscript{4,21}

The cause for the abnormal electrical repolarization is unknown. This study would suggest that there could be an inborn error of metabolism located in the mitochondria. Other postulates include the following: (1) abnormal asymmetric sympathetic stimulation to the left ventricle, decreasing the threshold for ventricular fibrillation;\textsuperscript{6,18,19,23} (such a mechanism may account for the abnormalities in repolarization seen with cerebrovascular problems); (2) abnormalities of the Purkinje fibers\textsuperscript{24} (however, there is little evidence to implicate the Purkinje system in myocardial repolarization); (3) potassium or calcium deficiency (however, there has been no support for this in spite of numerous electrolyte determinations, and there has been no improvement after potassium and calcium therapy in these patients); (4) central nervous system abnormalities; and (5) hereditary abnormalities of small coronary arteries.\textsuperscript{25}

At this time the most logical etiology for the syndrome of prolonged Q-T interval appears to be related to asymmetric, nonhomogeneous sympathetic innervation of the heart, eg, decreased activity of the right stellate ganglion or increased activity of the left stellate ganglion, or both.\textsuperscript{6,15,18,23} In support of this premise,\textsuperscript{21} (1) the syncopal episodes are often precipitated by physical exercise or emotions, events known to increase sympathetic activity; (2) prolongation of the Q-T interval and episodes of alteration of the T wave can be reproduced by asymmetric alterations in sympathetic tone;\textsuperscript{6,15,19,23} and (3) the best therapeutic results have been obtained by antagonizing the effects of sympathetic activity on the heart with \( \beta \)-adrenergic blocking agents\textsuperscript{6,19} and/or by ablating the lower left stellate ganglion along with the first thoracic ganglia.\textsuperscript{6,13,19} This pathogenesis is appealing and thought-provoking, but not all of the complex aspects have been proven. The interrelationship, if any, between the premise of asymmetric sympathetic innervation and the pre-
ously mentioned pathologic findings is unknown; however, it has been established that catecholamines cause mitochondrial influx of calcium.14 The finding of intramitochondrial granules that probably represent calcium may be related to excessive β-adrenergic effect on the myocardium.

The cause of the syncopal episodes and sudden death is a ventricular arrhythmia. Ventricular fibrillation or asystole or both have been documented in nine patients. The cause of the ventricular arrhythmia is probably related to the abnormality in repolarization allowing an atrial or ventricular premature beat to arrive in the vulnerable period; or as the heart rate increases during exertional or emotional stress, the normally conducted sinus stimulus arrives during the vulnerable period.

Until recently, no effective therapy was known for these patients. Administration of digitals or diphenylhydantoin would decrease the number and severity of attacks.26 A good result was obtained in three patients after a unilateral cervicothoracic sympathetic ganglionectomy.5,13,19 A study of one patient and his family using many pharmacologic agents showed that propranolol was the only agent effective in preventing ventricular fibrillation.25 In a recent review article on the syndrome of prolonged Q-T interval, Schwartz and associates6 listed all of the 203 unequivocal diagnosed cases of the syndrome of prolonged Q-T interval. When the treatment and outcome were known, 41 (73 percent) of 56 untreated patients died, seven (84 percent) of 11 patients treated without β-adrenergic blocking agents died, five (6 percent) of 79 patients treated with β-adrenergic blocking agents died, and none of the three patients having left sympathectomy died.

Since 85 percent of these cases have been reported in the last five years, the syndrome of prolonged Q-T interval may be more unrecognized than rare.6 The recognition of such cases is paramount, since therapy is available, and the treatment of choice is β-adrenergic blockade, eg, propranolol. Adequate dosage is important; and determinations of plasma levels of propranolol, where available, may be helpful. If propranolol therapy is unsuccessful in abolishing syncopal episodes, left stelllectomy,19 in addition to continuation of propranolol therapy, should be considered.

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