Heritable Q-T Prolongation Without Deafness

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SUMMARY
The family, reported on, have a syndrome of prolonged Q-T interval, potentially fatal episodes of ventricular arrhythmias, and normal hearing. The direct familial transmission demonstrated in this pedigree is consistent with an autosomal dominant mode of inheritance. To protect other members of the family from the consequences of ventricular arrhythmia experienced by the irreversibly brain-damaged index patient, a series of physiologic investigations was undertaken on this patient in a search for a suitable prophylactic medical regimen. The attacks of ventricular arrhythmia were found to be precipitated by increase in systemic pressure, sinus tachycardia, and extrasystoles occurring in the supernormal phase of repolarization (R in T syndrome). Propranolol was demonstrated to be an effective agent in preventing the ventricular arrhythmia in the index case and in other family members. Since administration of the beta-adrenergic blocker isoproterenol did not produce ventricular fibrillation, it is assumed that the action of propranolol in preventing ventricular arrhythmia is not mediated through beta-adrenergic blockade, but through its direct antiarrhythmic properties. The subject experienced no ill effect from the series of investigations.

Additional Indexing Words:
Ventricular arrhythmia  Isoproterenol  Propranolol

A SYNDROME characterized by potentially fatal repetitive episodes of ventricular arrhythmias, a prolonged Q-T interval on the electrocardiogram, and deaf-mutism was first described in 1957 by Jervell and Lange-Nielsen.1, 2 These families and others3 with deaf-mutism presented with an autosomal recessive pattern of inheritance.
Later Romano and his associates4 and Ward5 described families having a prolonged Q-T interval in which sudden death also occurred. In these and other similar families, however, hearing was normal, and direct familial transmission was consistent with an autosomal dominant mode of inheritance.4-7

This report concerns a family (fig. 1) in which a mother and two of her four sons have a prolonged Q-T interval and have had repeated episodes of loss of consciousness associated with ventricular tachycardia or fibrillation. Their hearing and mental development are normal. The maternal grandmother is also reported to have a history of fainting episodes as a child which disappeared in adulthood, but her ECG is normal at present.

Report of Cases
Case 1. JAH
The 3-year-old boy was comatose, on admission to the Texas Children's Hospital on March 9, 1968, following cardiac arrest and resuscitation by the mother. He has never regained consciousness and neurologic evaluation indicates irreversible brain damage.
At 20 months of age the first of the syncopal attacks began, each initiated by excitement or physical stress. He fully recovered from the early episodes without neurologic damage. The attacks

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were diagnosed as "breath holding" spells or "hypoxic crises," and diphenylhydantoïn and phenobarbital had been prescribed without apparent benefit.

On admission, the child was unconscious and unresponsive to stimuli; the pupils were constricted; the respiratory rate was 30/min; the pulse rate, 80/min; and the blood pressure, 110/80. The heart was not enlarged; there was no significant murmur; and the heart sounds were normal. The lungs were clear.

The concentration of hemoglobin was 13.8 g/100 ml; the hematocrit was 44%; serum sodium, 140 mEq/L; potassium, 4.1 mEq/L; chloride, 101 mEq/L; CO₂, 11.5 mEq/L; fasting blood sugar, 105 mg/100 ml; calcium, 9.5 mg/100 ml; phosphorus, 3.9 mg/100 ml. The electrocardiogram showed sinus rhythm with a prolonged Q-T interval and biphasic T waves in all the limb leads (fig. 2).

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**Figure 1**

Pedigree of family H.

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**Figure 2**

Electrocardiogram of case 1 shows prolonged Q-T interval (Q-T = 0.44; Q-T₁ = 0.28; Q-T/Q-T₁ ratio = 1.50) and diphasic T waves in all the limb leads, with abnormal positive T waves in right precordial leads.
HERITABLE Q-T PROLONGATION

During the first 2 weeks of observation 85 episodes of ventricular fibrillation occurred. On two occasions the ventricular fibrillation converted spontaneously to sinus rhythm within a few seconds; other episodes of ventricular fibrillation were converted electrically to sinus rhythm.

At various times the following types of medication were employed unsuccessfully in an effort to prevent the arrhythmia from recurring: digitalis; diphenylhydantoin; glucose, potassium, and insulin solution of Sodi-Pallares and his coworkers; lidocaine; diazepam; and calcium.

During observation the ECG was monitored on tape for six periods of 10 hours each. The T wave changed from tall and peaked to low voltage and notched, but with each change the Q-T interval remained prolonged, without change in the QRS complex. Following digitalization the Q-T interval shortened and the T-wave morphology became more normal (fig. 3). However, the patient continued to have episodes of ventricular fibrillation.

Figure 3

Electrocardiogram of case 1 after digitalis, the Q-T interval is shortened (Q-T = 0.36; Q-Tc = 0.30; the Q-T/Q-Tc ratio = 1.20) and the T waves in right precordial leads are now morphologically normal.

Figure 4

Electrocardiogram of case 2. Before exercise Q-T = 0.42; Q-Tc = 0.36; Q-T/Q-Tc = 1.16. After exercise Q-T = 0.42; Q-Tc = 0.30; and the Q-T/Q-Tc ratio is increased to 1.40.
Case 2. BH

The brother of patient 1, who is 11 years old, has had 20 to 25 episodes similar to those described in his sibling. At the age of 4 years, while swimming, he had his first episode of loss of consciousness. Mouth-to-mouth resuscitation was given, and he regained consciousness in 1 min. Each of these episodes has been associated with swimming, running, or bicycling. He always swims with relatives near at hand who are ready to give him artificial respiration if needed. The resting electrocardiogram showed slight Q-T interval prolongation which became further prolonged after exercise (fig. 4). The chest x-rays were normal.

Case 3. ADH

This 38-year-old female, the mother of the first two patients, has had three episodes of loss of consciousness (at ages 12, 16, and 36 years), all of them after vigorous exercise. She is aware of the danger of loss of consciousness and guards against overexerting herself. A prolonged Q-T interval is present on the resting electrocardiogram with a Q-T/Q-Tc = 1.15. Her other two children, 6 and 8-year-old boys, have had no syncopal attacks, have normal resting and exercise electrocardiograms, and normal hearing.

Physiologic Investigation

To protect the other family members from the disastrous consequences of ventricular arrhythmia experienced by our first patient, a series of investigations was undertaken in a search for a suitable prophylactic medical regimen in the irreversibly brain-damaged patient.

The studies of Fastier and Smirk,9 in dogs and cats, demonstrated that amarin (2:4:5 triphenyldihydroiminazole) produced a prolongation of the Q-T interval in cats and dogs, with no change in the blood level of calcium or potassium. In these experimental animals, when epinephrine was injected intravenously in small amounts (5 μg/kg), ventricular fibrillation was produced.

In an effort to determine if our brain-damaged patient would demonstrate a similar response to epinephrine, we administered 5 μg/kg intravenously (fig. 5) in a single bolus, and it did produce ventricular fibrillation. Resuscitative equipment was at hand,
Ventricular fibrillation produced after infusion of phenylephrine, 0.1 mg/kg.

and the arrhythmia was converted to sinus rhythm within 10 seconds. In a similar manner, an alpha-adrenergic stimulator (phenylephrine, 0.1 mg/kg) was administered (fig. 6), and fibrillation was again produced. A beta-adrenergic stimulator (isoproterenol, 0.5 μg/kg) was administered intravenously (fig. 7), but in spite of marked tachycardia, fibrillation was not produced. However, with this drug a new reaction was observed, a rate related shortening of the Q-T interval (as in normal subjects). Acetylcholine was administered in a dose of 3 mg/kg, and a severe asthmatic episode was observed with no change in the ECG.

Three subsequent courses of administration of these same drugs were given following premedication with atropine (0.01 mg/kg), an alpha-adrenergic blocking agent (phenylephrine, 0.1 mg/kg), and a beta-adrenergic blocking agent (propranolol, 1 mg given intravenously).

Epinephrine produced ventricular fibrillation after the administration of both atropine and phentolamine. In this last course, a femoral intra-arterial pressure monitor recorded extrasystoles which were apparently pressure-related (fig. 8). Fibrillation occurred when the pressure reached the 180 mm Hg level (fig. 9). A difference between the ECG during the induction of fibrillation by epinephrine alone (fig. 5) and the present tracings (figs. 8 and 9) is that after the alpha-adrenergic blocking agent the T waves did not peak (this observation possibly suggests the absence of hyperpotassemia).

Propranolol, 1 mg, was given intravenously and fibrillation was not produced by the subsequent administration of epinephrine. The administration of isoproterenol, however,
GARZA ET AL.

Figure 7
Isoproterenol given in a single bolus of 0.5 μg/kg. Fibrillation was not produced and the Q-T interval shortened in relation to the increase in heart rate.

did not produce ventricular fibrillation so it is assumed that this action of propranolol in preventing ventricular arrhythmia is not mediated through beta-adrenergic blockade but through its direct antiarrhythmic properties.\(^1\)

The preceding study demonstrated that ventricular arrhythmia was precipitated by three different mechanisms: (1) an increase in the systemic blood pressure (pressure induced extrasystoles); (2) sinus tachycardia (when the impulse reaches the ventricles still in a depolarized state); and (3) an extrasystole produced in the supernormal phase of repolarization (R in T syndrome).

Discussion
Etiologic considerations regarding the prolonged Q-T interval have included: (1) vagal disturbance;\(^15\) (2) absence or anomaly of the Purkinje fibers;\(^13,14\) (3) asymmetrical sympathetic neural stimulation of the ventricular myocardium;\(^15\) and (4) incapacity for normal repolarization of the myocardium due to a metabolic abnormality.\(^16\)

The effect of the vagal influence is to slow or stop sinus impulse formation and to produce A-V conduction delay or block. Syncope produced by reflex vagal activity is usually associated with asystole rather than ventricular fibrillation. Vagal activity could act indirectly to prolong the Q-T interval through its effect on heart rate. In our cases, however, the Q-T interval remained prolonged and was independent of the R-R interval.

If, on the other hand, the prolongation of the Q-T interval were due to the absence of

Figure 8
After phentolamine, 0.1 mg/kg, was given I.V. in case 1, epinephrine, 0.005 mg/kg, was given. Pressure related extrasystoles were recorded.

Figure 9
After phentolamine, 0.1 mg/kg, was given I.V., 0.005 mg/kg of epinephrine was injected I.V., and fibrillation was produced when systemic blood pressure reached the 180 mm Hg level.
Purkinje fibers, the QRS complex should be widened and the conduction abnormality should remain relatively constant rather than variable as it did in our patients.

Asymmetrical neural stimulation of the myocardium has been demonstrated in the dog to produce changes in the Q-T interval and the T-wave similar to those found in our patients. It is not, however, possible to duplicate in the human subject the studies of Yanowitz and associates.15

The last possibility, that of an underlying metabolic disturbance, is the explanation most consistent with the findings derived from the present experimental design. A metabolic abnormality is suggested by the occurrence of alternately positive and negative T waves (fig. 10) and the marked variability in configuration of the T waves at different times of the day (fig. 11), which could represent variability in repolarization secondary to changing functional demands of the heart.

The last part of phase 3 in the monophasic action potential corresponds to the supernormal phase in which the myocardium is hyperirritable.17 An extrasystole reaching the heart at this moment could produce an episode of ventricular tachycardia or fibrillation (fig. 12). This phenomenon, seen in the ECG, is known as the "R-in-T" syndrome and has been described by Smirk and Palmer18 and Dolara.19

Treatment with digitalis has been advocated for patients with a prolonged Q-T interval. Digitalis decreased the Q-T interval in our patient and changed the T-wave morphology but did not prevent episodes of ventricular fibrillation.

The stimulus which starts the arrhythmia under physiologic conditions is usually vigor-
ous exercise, such as swimming and running (cases 1, 2 and 3) or excitement (case 1). With the development of tachycardia in these cases, the Q-T interval either remains the same or becomes even more prolonged, while the P wave moves over the T wave and the P-R interval becomes shorter. Thus, at the moment the atrial stimulus reaches the ventricles in the supernormal phase, the arrhythmia is produced.

In 1964, Gamstorp and associates reported a family with prolonged Q-T interval, cardiac arrhythmias, and hypopotassemia without deafness. These patients improved with the administration of potassium. All of our patients have normal levels of serum potassium, and the arrhythmia in our index case was not prevented by administration of potassium.

The evidence of direct transmission in all families with prolonged Q-T interval and normal hearing, consistent with autosomal dominant inheritance, leads the authors to propose that this is a syndrome distinct from the Jervell and Lange-Nielsen syndrome which follows an autosomal recessive pattern and has the additional defect of congenital deafness.

The demonstration of the efficacy of propranolol in preventing ventricular arrhythmia in the index case appeared to provide the answer for a prophylactic drug for affected members of this family. After determination of the optimal oral dosage for each patient, they have all been maintained free of arrhythmias.

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Figure 11

The morphology of the T waves of case 1 varied at different hours of the day.
HERITABLE Q-T PROLONGATION

Figure 12

An episode of ventricular tachycardia was produced in case 1, when a ventricular complex occurred during the late part of the T wave (R in T syndrome).

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Let us pass from the pitfalls of plausibility to the equally misleading failures due to an ignorance of the laws of probability. We cannot rely upon good horse sense in such matters. What do you think are the probabilities that at a dinner attended by twenty people there will be at least one pair who share the same day of the same month as their birthday? Are you surprised to know that it is better than a 50-50 chance? More precisely it is a 52.05 chance. Does that disturb your confidence in your common sense? It did mine.—Alan Gregg: For Future Doctors. Chicago, University of Chicago Press, 1957, p. 85.
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