

# Hereditary prolongation of QT interval

## *Study of two families*<sup>1</sup>

G. E. Gale, C. K. Bosman, R. B. K. Tucker, and J. B. Barlow

*From the Cardiovascular Research Unit, Department of Medicine, University of the Witwatersrand; and the Cardiac Clinic, General Hospital, Johannesburg, South Africa*

*A syndrome has previously been recognized, which is characterized by recurrent episodes of loss of consciousness, some of which end fatally. The electrocardiogram in affected subjects shows prolongation of the QT interval.*

*In the present study, 2 unrelated families with a total membership of 82 were investigated; 30 living subjects were examined and 20 were found to be affected. A further 14 members, 11 of whom died suddenly, were presumed from their histories to have been affected. The condition seems to be much more common, at least in South Africa, than the small number of previously reported cases would suggest.*

*In contrast to the similar syndrome in which congenital deafness is also a feature and in which the disorder is transmitted in an autosomal recessive manner, analysis of the present data reveals an autosomal dominant inheritance with variable penetrance. The fundamental nature of the disorder remains unknown. Though treatment is generally unsatisfactory, beta-adrenergic blocking agents may be of value.*

The uncommon association in childhood between congenital perceptive deafness, a prolonged QT interval on the electrocardiogram, and a liability to syncopal attacks, sometimes fatal, was first reported in 1957 by Jervell and Lange-Nielsen. To date, a total of 17 such patients has been described (Levine and Woodworth, 1958; Fraser, Froggatt, and James, 1964a; Fraser, Froggatt, and Murphy, 1964b; Jervell, Thingstad, and Endsjö, 1966). Nine similar patients, but without deafness, have been described in detail (Romano, Gemme, and Pongiglione, 1963; Ward, 1964; Gamstorp, Nilsén, and Westling, 1964), and 2 such families in South Africa, apparently unrelated, have been briefly reported from this laboratory (Barlow, Bosman, and Cochran, 1964) and by other workers (Combrink and Kloppers, 1965). Though the numbers are small, the clinical and family histories suggest that the syndrome without deafness represents a different genotype. This paper supplies further details of the family quoted originally by Barlow *et al.* (1964) and describes another family which we have since

encountered. A total of 34 cases is included in this study. This number, together with J. M. Combrink's (1969, personal communication) experience of 8 patients, suggests that the condition may not be uncommon; though possibly only in this country.

### Subjects

In the first family (A) (Fig. 1), the proposita was a 36-year-old woman who had had episodes of unconsciousness since the age of 3 years. As a child she had witnessed similar episodes in her mother and a sister, which eventually ended in their deaths at the ages of 33 and 17 years, respectively. Four of her 6 living sibs had also suffered from these episodes, as had all her 4 living children. Her fifth child, a boy aged 12 years, had died suddenly after running. The family pedigree (Fig. 1) shows that this woman's great uncle, who died suddenly at the age of 16 years, and 25 of her grandfather's 66 descendants are known or reasonably presumed to be similarly affected.

The attacks of unconsciousness usually start in infancy or early childhood and tend to become less frequent or disappear in adulthood. They are often precipitated by fright, anger, or strenuous exercise. An aura of a fluttering sensation in the chest and a feeling of lightheadedness may precede the loss of consciousness. The subject may be unconscious for a few seconds or several minutes

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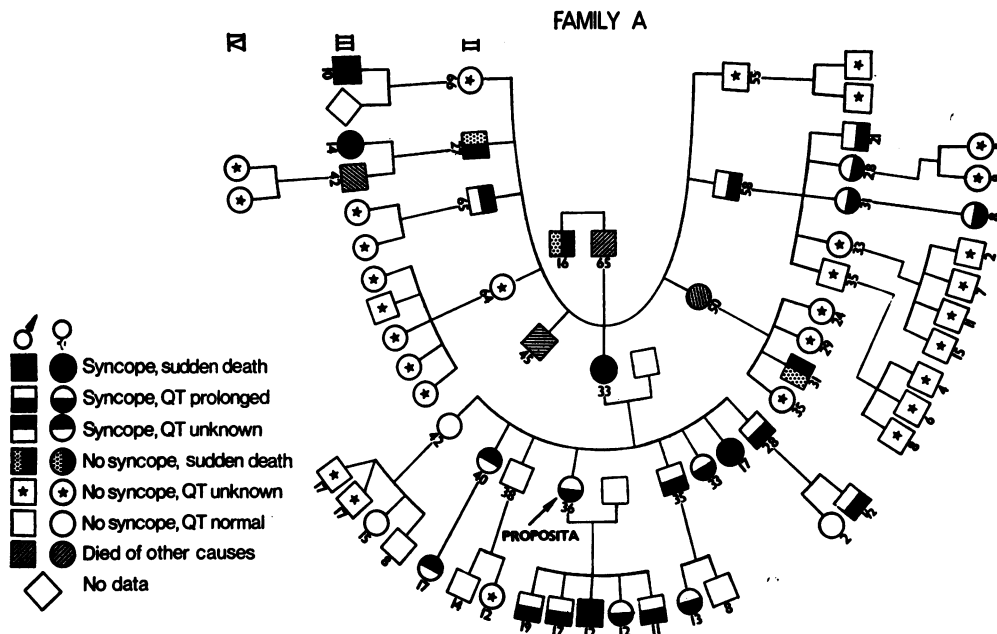


FIG. 1 Pedigree of Family A: 26 of 68 members are affected. Numbers denote age in years and Roman numerals generations. The first generation is not marked.

and, according to observers, because we have not personally witnessed any attacks, becomes pale, is occasionally incontinent, and the limbs may be flaccid, tonic, or show convulsive movements. The pulse is impalpable but on recovery of consciousness is reputedly rapid. Episodes occur irregularly at intervals ranging from 2 months to a year. Some members of the family are more frequently and more severely affected than others.

The second family (B) (Fig. 2) was, as far as could be ascertained, unrelated to the first, though consanguinity is possible since both originated from the same district. It comprised 14 members in 4 generations, of whom 8 had electrocardiographic or historical evidence of the syndrome. The propositus was a 9-year-old boy who had had 5 syncopal attacks since the age of 3 years. These always occurred while he was running. A brother and maternal aunt had died in similar attacks at the ages of 6 and 9 years, respectively.

In neither family has clinical examination of any patient between attacks revealed any cardiovascular abnormality. Electrocardiograms were recorded in 30 subjects and the QT intervals were determined, following the method of Lipeschkin and Surawicz (1952), by taking the mean value of 4 consecutive complexes in each of the 3 leads in which the T wave was most clearly defined. Twenty cases showed prolongation of the QT interval (Table and Fig. 3) according to the criteria of Bazett (1920) and Ashman and Hull (1941). All the members of family A who had this electrocardiographic abnormality had had syn-

copal attacks, whereas 3 of the 5 members of family B with prolonged QT intervals had no history of syncope. Mechanical systole, measured from the Q wave of the simultaneous electrocardiogram to the onset of the second sound (McKusick, 1958), was normal in the 7 patients with prolonged QT intervals on whom phonocardiograms were performed (Table and Fig. 4). Serum concentrations of sodium, potassium, calcium, inorganic phosphate, chloride and bicarbonate were estimated in 8 patients and the serum magnesium in 3: all were normal. One affected 3-year-old child had a mild hypochromic anaemia with a haemoglobin concentration of 9.4 g./100 ml. Five patients had normal audiograms and none was deaf on clinical testing. Electroencephalograms in 3 patients were normal.

## Discussion

The QT interval varies with heart rate, sex, and age. Numerous formulae have been derived to define its limits of normality but the QT prolongation in nearly all of our cases is so great that it is pathological by any standard. In many instances it varied from time to time and in a few was nearly normal on occasion (Fig. 5). Our experience confirms that of Jervell and Lange-Nielsen (1957), who found no correlation between the degree of QT prolongation and either the number or severity of syncopal attacks. On the other hand, Fraser *et al.* (1964a), while agreeing that the degree of prolongation does not correlate with the severity of attacks, believe that greater prolongation is associated with both an earlier

age of onset and increased frequency of attacks. Abnormalities of the T waves themselves have also been observed (Levine and Woodworth, 1958; Romano *et al.*, 1963; Fraser *et al.*, 1964a; Ward, 1964), and include large, bifid, biphasic, or inverted forms. Upward sloping of the ST segment is not uncommon (Fig. 3) and the inversion of T waves may be transient (Fig. 5).

The fundamental nature of the disorder is unknown. Atrioventricular conduction and the duration of mechanical systole are normal. It has been postulated (Ward, 1964) that an abnormality of myocardial metabolism prolongs repolarization after systole. Sympathetic stimulation sometimes prolongs the QT interval (Yanowitz, Preston, and Abildskov, 1966), and it is possible that the myocardium in these patients is unduly sensitive to catecholamine release.

Episodes of loss of consciousness invariably begin in early childhood or infancy, and most patients with the complete syndrome have had episodes before the age of 4 years. All but 1 of the 11 fatal cases hitherto reported have died in childhood or infancy, but our first family pedigree provides evidence that deaths also occur in adulthood. Nevertheless, syncope is certainly less frequent and may disappear in surviving adults. Our second family (B) had 3 members (aged 7, 40, and 76 years, respectively) with prolonged QT intervals who denied ever having had syncope.

We have not personally witnessed any such episodes but they have been shown electrocardiographically in some instances to result from ventricular fibrillation (Romano *et al.*, 1963; Ward, 1964). Fraser *et al.* (1964a) noted that one of their patients was pulseless. Prolongation of the QT interval increases the chances of an ectopic beat falling on the vulnerable period of the preceding T wave and thus precipitating ventricular fibrillation. Other observers (Levine and Woodworth 1958; Jervell *et al.*, 1966) of syncopal episodes, however, found the pulse normal. It is indeed difficult to account for syncope in those patients with a normal pulse but possibly brief, unobserved, ventricular fibrillation preceded the observation of a normal pulse in these instances.

It has been suggested (Schamroth, 1969) that in this syndrome there is a state of inequality of the QT interval in different parts of the myocardium and that asynchronous refractoriness predisposes the myocardium to ventricular fibrillation by a critically timed early impulse occurring during a vulnerable out-of-phase state. Such electrical asymmetry would not be manifested by the scalar electro-

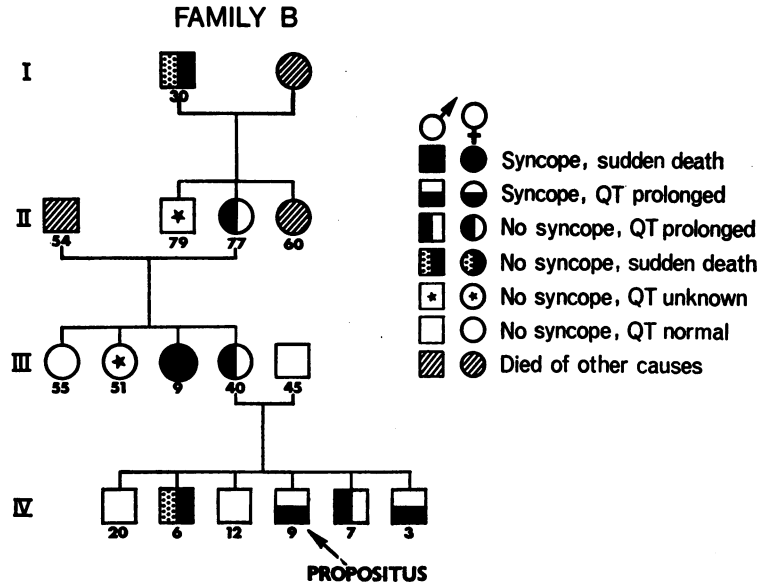


FIG. 2 Pedigree of Family B: 8 of 14 members are affected. Numbers denote age in years and Roman numerals generations.

TABLE Electrocardiographic and phonocardiographic time intervals in 20 observed abnormal members of both families

Patient	Age (yr.)	Sex	RR (sec.)	QT (sec.)	QT <sub>c</sub> * (sec.)	QA (sec.)†
<i>Family A</i>						
MB	36	F	0.82	0.47	0.52	0.38
JB	17	M	0.60	0.38	0.49	0.38
FB	19	M	0.65	0.36	0.45	0.39
RB	12	F	0.81	0.48	0.53	0.36
HB	11	M	0.73	0.38	0.44	0.37
YR	33	F	0.60	0.43	0.55	
CR	13	F	0.82	0.43	0.48	
HR	35	M	0.70	0.39	0.47	
RR	28	M	0.81	0.40	0.45	
DR	‡	F	0.55	0.35	0.47	
Mr. T	58	M	0.68	0.38	0.46	
JT	21	M	0.95	0.47	0.48	
Mrs. R	31	F	0.83	0.45	0.49	
GR	8	F	0.57	0.39	0.51	
Mrs. L	28	F	0.62	0.40	0.50	
<i>Family B</i>						
Mrs. B	40	F	0.79	0.45	0.51	
MB	9	M	0.76	0.43	0.49	0.35
RB	7	M	0.82	0.47	0.52	0.37
CB	3	M	0.70	0.40	0.48	
Mrs. C	76	F	0.65	0.41	0.51	

\* Bazett's (1920) formula. Upper limits of normal according to Ashman and Hull (1941): 0.432 for women and 0.422 for men and children.

† QA = interval between Q wave and aortic component of second sound.

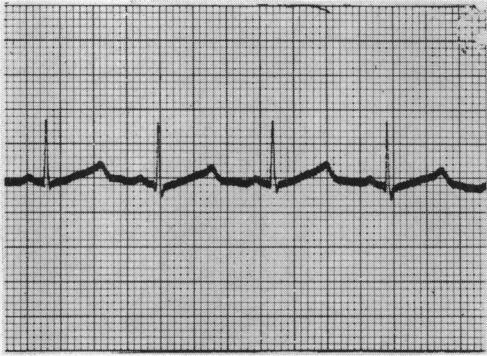


FIG. 3 Standard lead II electrocardiogram of a 3-year-old boy showing typical prolongation of the QT interval. Note the upward sloping ST segment.  $QT = 0.40$  sec.  $RR = 0.69$  sec.  $QT_c = 0.48$ .

cardiogram since it reflects only the longest QT interval (Schamroth, 1969).

Hypokalaemia was found in one instance by Gamstorp *et al.* (1964), but other serum electrolyte disturbances have not been reported by others or detected by us. Blood sugar concentrations have been consistently normal - in one of our patients this estimation was made within five minutes of a syncopal episode.

No myocardial pathology has yet been consistently demonstrated histologically. In their 2 fatal cases with associated deafness, Fraser *et al.* (1964a) observed foci of haemorrhage, fibrosis, and fatty infiltration in the region of the sino-atrial node, and noted that the Purkinje fibres were difficult to define. No histological abnormality was detected, however, in 5 other patients, 2 of whom were not deaf (Jervell and Lange-Nielsen, 1957; Levine and Woodworth, 1958; Fraser *et al.*, 1964a; Ward, 1964; J. M. Combrink, 1969, personal communication).

We have assumed that there was a prolonged QT interval in the unobserved members of our 2 families who either had repeated syncopal attacks or died suddenly at a young age. The genetic pattern is thus one of an autosomal dominant inheritance with variable penetrance and contrasts with the recessive inheritance found in the cases with deafness (Fraser *et al.*, 1964b).

The management of these patients is difficult and the optimal therapy not yet established. Severe physical exertion and emotional disturbances should be avoided as far as is possible. Several drugs should theoretically be of value: digitalis to shorten the QT interval, a beta-receptor blocking agent to reduce

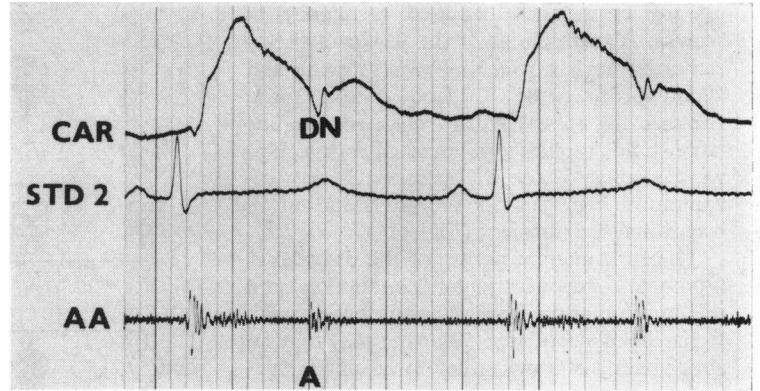
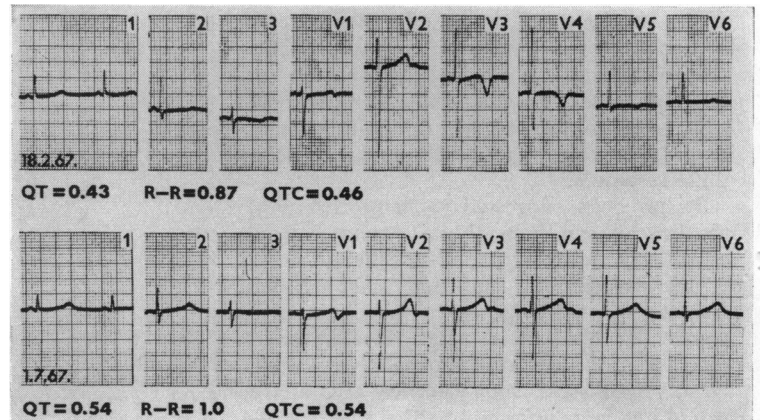


FIG. 4 Simultaneous carotid pulse tracing (CAR), electrocardiogram (STD2), and phonocardiogram recorded at the aortic area (AA). Electrical systole is prolonged with a QT interval of 0.46 sec. when the RR interval is 0.84 sec. Mechanical systole is of normal duration, measured by the QA interval of 0.36 sec. The very early position of the aortic closure sound (A) in relation to the T wave of the simultaneous electrocardiogram is well shown. DN = dicotic notch. Time intervals 0.04 sec.

FIG. 5 Serial electrocardiograms of a 7-year-old boy showing, before treatment (18.2.67), slight prolongation of the QT interval and deep symmetrical inversion of the T waves in the mid-precordial leads; and 5 months later, after treatment with digoxin and potassium (1.7.67), further prolongation of the QT interval, a sloping ST segment, and upright T waves. QT and RR intervals expressed in seconds.



adrenergic hyperactivity, and a sedative to control emotional hyperreaction. Jervell *et al.* (1966) achieved reduction in the QT interval to normal lengths by the administration of digoxin and in 2 of their 3 cases the number of syncopal episodes decreased. Ward (1964) claimed temporary improvement with guanethidine and conspicuous improvement with pronethalol. Gamstorp *et al.* (1964) achieved temporary success in their hypokalaemic patient with potassium administration. James (1969) suggested that phenytoin and phenobarbitone might be of value but had no evidence to confirm this. He also warned that electronic pacing to prevent tachyarrhythmia might be dangerous.

Drug therapy in our family A was initially digoxin and potassium chloride. This medication neither reduced the QT interval (Fig. 5) nor diminished the number or severity of the syncopal episodes. One patient was then given pronethalol which abolished his aura without affecting the frequency of the episodes, and he therefore stopped the drug. This family has unfortunately been extremely uncooperative and unreliable as far as taking tablets is concerned. We have been unable to contact many of them during the past 2 years, but, to our knowledge, no further deaths have occurred.

The 3 children of family B, aged 9, 7, and 3 years, respectively, have taken digoxin, potassium chloride, and chlordiazepoxide ('Librium') in usual doses for 2½ years. In the past 2 years propranolol has been added in initial divided daily doses of 30, 20, and 15 mg., respectively, increasing to 30 mg. in the 2 younger children. An attempt to increase the dose in the eldest child resulted in bradycardia. This treatment has been followed by definite improvement in the eldest child who subsequently had only one syncopal episode. The youngest child developed his first episode while on the initial therapy and has now had a total of 5, including 2 while on propranolol. The 7-year-old sib has never had syncope. In none of these 3 patients, nor in any members of family A, was the QT interval or T wave abnormality altered by therapy.

Thus, though it is not always effective, adrenergic beta-blockade probably affords the best method of treatment. The prognosis usually improves if the patient survives to adulthood.

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