

# Hereditary Dysrhythmic Congestive Cardiomyopathy

A. J. BRINK, M. TORRINGTON, J. J. VAN DER WALT

## SUMMARY

A patient with hereditary congestive cardiomyopathy, who presented with recurrent episodes of life-threatening ventricular arrhythmias most often precipitated by exercise, is described. The condition is marked by either a progressive course, in which case congestive cardiac failure may set in towards the end, or by unexpected sudden death.

The family tree could be traced for 10 generations. The information about the tenth generation firmly established that 4 members, 2 of whom had died, were affected. Other evidence suggests that the condition was the cause of death in 3 members of the eighth generation.

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Heart muscle dysfunction of unknown cause or association is generally referred to as cardiomyopathy. Clinical and pathological descriptions have so far laid emphasis on 3 forms: (i) a systolic pump failure characterised by signs and symptoms of congestive cardiac failure and a large dilated heart; (ii) diastolic compliance failure, characterised by gross hypertrophy of the ventricles and interventricular septum with or without outflow obstruction; and (iii) obliterative cardiomyopathy in which there is cavity obliteration or AV valve incompetence, or both.<sup>1-3</sup> The congestive and obliterative types have been particularly well documented from African countries.<sup>6-7</sup>

Familial forms of cardiomyopathy have been recognised but the pathological and clinical descriptions indicate that these are almost exclusively the hypertrophic variety.<sup>1,2,8-12</sup> The existence of a congestive form of familial cardiomyopathy has been suggested,<sup>12-14</sup> but it has not been recognised or clearly described as such. In this article we describe a patient with an hereditary cardiomyopathy, which presented with life-threatening ventricular arrhythmias and which on autopsy proved to be of the congestive or dilated type.

The family tree could be traced for 10 generations. The information in the tenth generation firmly established that 4 members, 2 of whom have died, were affected. Other evidence suggests that the condition was the cause of death in 3 members in the eighth generation.

Cardiac Unit, Department of Internal Medicine, University of Stellenbosch and Tygerberg Hospital, Parowvallei, CP

A. J. BRINK, M.D., F.R.C.P., D.S.C.

National Research Institute for Nutritional Diseases, South African Medical Research Council, Parowvallei, CP

M. TORRINGTON, M.SOC.SC.

Department of Anatomical Pathology, University of Stellenbosch and Tygerberg Hospital, Parowvallei, CP

J. J. VAN DER WALT, M.B. CH.B., M.MED. (PATH.), M.D.

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## CASE REPORT

A 13-year-old girl was admitted to hospital 3 hours after having suffered a sudden loss of consciousness associated with respiratory arrest and circulatory collapse. The rapid application of external cardiac massage and mouth-to-mouth respiration by a trained nurse enabled the patient to reach the hospital alive.

In the cardiac intensive care unit it was established that she had ventricular tachy-arrhythmia. The patient had a stormy hospital course with repeated ventricular arrhythmias, including bouts of ventricular fibrillation, and had repeated direct-current shock therapy. The arrhythmias were extremely resistant to treatment with all forms of anti-arrhythmic drugs. An attempt to overdrive the ventricles by means of a pacemaker was also ineffective and had to be discontinued. Partial control of the arrhythmia was eventually achieved by a combination of digoxin, propranolol, quinidine sulphate and diphenylhydantoin. Her condition improved to the extent that she could be discharged from hospital 2 months after admission.

In between the episodes of acute ventricular dysrhythmia the patient's physical condition was normal. Blood pressure was 110/70 mmHg and all pulses were normally present and palpable. The heart size and sounds were initially normal. However, an ECG showed evidence of a first-degree heart block, low amplitude QRS complexes, pathological T-wave changes and a prolonged QT<sub>c</sub> interval, which at different times varied from 0.43 seconds to as long as 0.53 seconds (Fig. 1). The patient's parents said that they had unexpectedly lost a son at the age of 15 years, a year before the admission of their daughter. The son had suddenly collapsed and died during physical activity.

Regular follow-up of the patient revealed that frequent episodes of dizziness and even mild syncope recurred

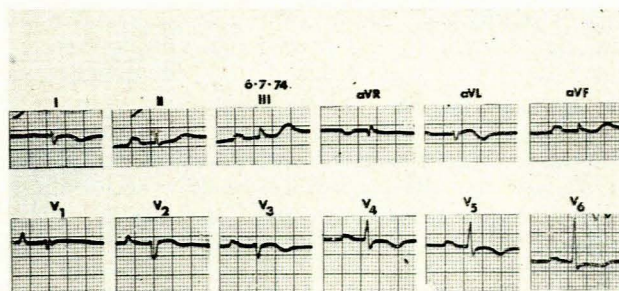


Fig. 1. ECG of proband showing first-degree heart block, low voltage complexes, ST-segment and T-wave abnormality and prolonged QT<sub>c</sub>.



despite the therapy. These episodes were precipitated by physical activity.

Because it was thought possible that the prolonged QT<sub>c</sub> interval might reflect the underlying cause of the ventricular tachy-arrhythmias, the QT<sub>c</sub> interval was studied after stellate ganglion block.<sup>15</sup> A left cervical ganglionectomy was done on the strength of these studies. For a time it was thought that mild improvement had occurred, but this idea was soon dispelled. For some months the more serious ventricular rhythm disturbances abated and a supraventricular arrhythmia resembling an atrial flutter appeared periodically.

Two years after the initial observations, clinical and radiological evidence showed that cardiac enlargement was taking place (Fig. 2). A third heart sound was audible and a murmur indicating mitral incompetence appeared. Crises of ventricular tachy-arrhythmia again supervened (Fig. 3) and she was repeatedly admitted to hospital. Progressive cardiac enlargement (Fig. 2) and an increasing degree of impairment of effort tolerance occurred and eventually left ventricular failure supervened. The patient died 4 years after first coming under observation, in a condition of cardiac failure and with persisting crises of ventricular arrhythmia.

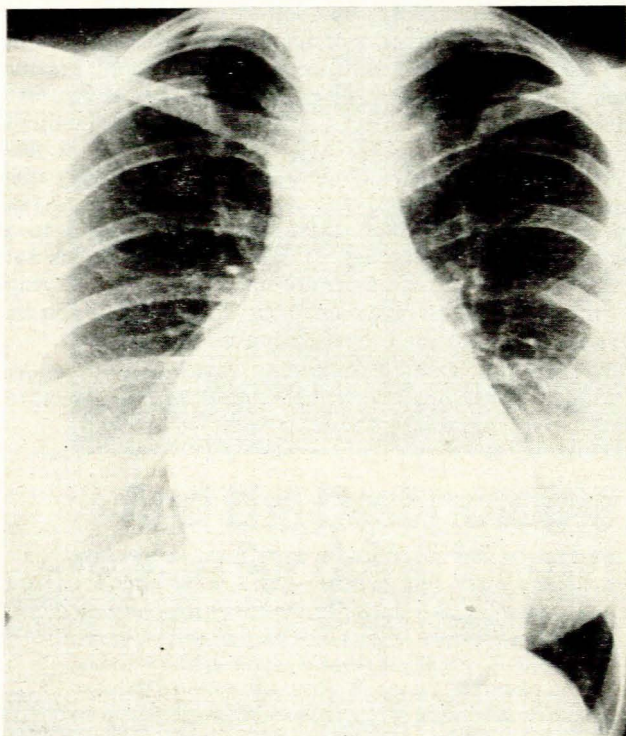


Fig. 2. Chest radiograph of proband showing cardiac enlargement.

## AUTOPSY FINDINGS

### Macroscopic Examination

Autopsy consent was limited to an examination of the heart only. Generalised cardiomegaly was present due to

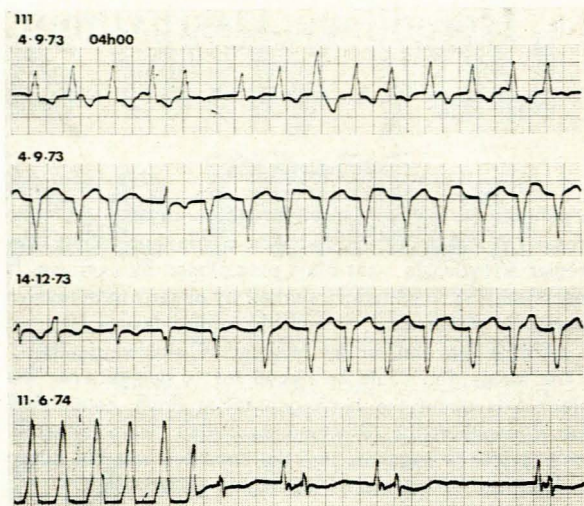


Fig. 3. ECG rhythm strips from proband showing ventricular tachy-arrhythmia.

hypertrophy and dilatation of all the chambers. The dilatation was more marked on the right side of the heart, but it masked hypertrophy on both sides. However, the hypertrophy was reflected in the heart weight of 482 g. There was no asymmetrical septal hypertrophy. The parietal endocardium of the left atrium and left ventricle showed foci of mild thickening. Organising thrombi were present in the right atrium as well as in both ventricles. There were no valvular abnormalities.

### Microscopic Examination

The myocardial fibres were regularly arranged and were hypertrophied but attenuated. A moderate degree of nuclear pleomorphism was present, but there were no perinuclear haloes or glycogen pools.<sup>16</sup> Occasional myofibres showed basophilic degeneration. Small foci of active myocytolysis were present in relation to mural thrombi or focal endocardial thickening. All chambers showed slight focal fibro-

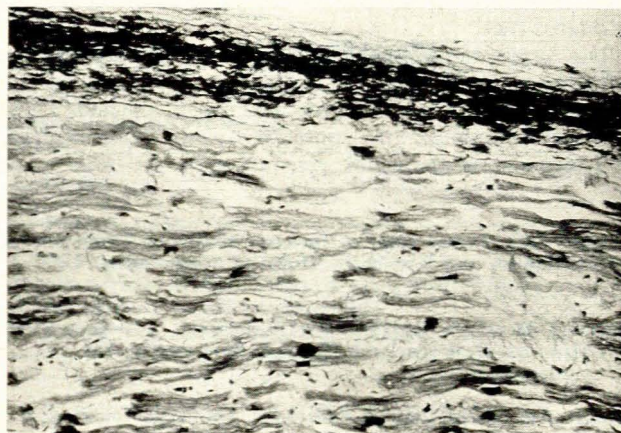


Fig. 4. Endocardial fibro-elastosis and active myocytolysis. Note pleomorphic nuclei (Verhoeff  $\times$  200).



elastotic thickening of the parietal endocardium (Fig. 4). Small stellate areas of connective tissue increase were present subendocardially (Fig. 5). Vessels included in the sections were normal. The conduction system was dissected according to the method of Hudson,<sup>27</sup> but no lesions of the conducting tissues could be demonstrated.

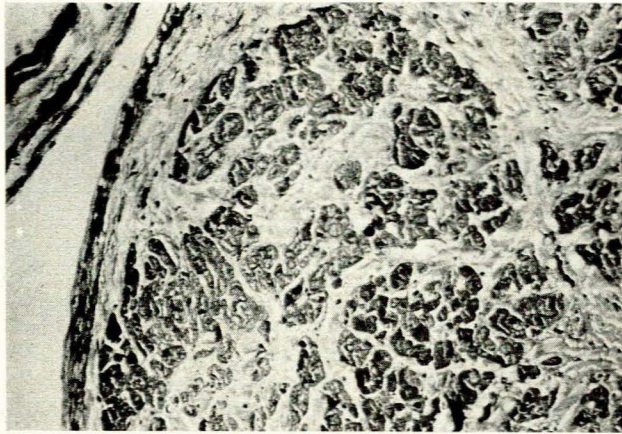


Fig. 5. Endocardial fibro-elastosis, myofibre hypertrophy and interstitial stellate scars (Verhoeff  $\times 200$ ).

### FAMILY HISTORY

During an interview with the parents of the proband, it was suggested by the father that 2 teenage sisters 'somehow related to him' were affected with a condition similar to that of his daughter. The parents of the affected children were traced, and by means of further interviews and with the assistance of the Cape Town Dutch Reformed Church Archives it was possible to show that the 2 girls, aged at this time 20 and 21 years respectively, were related through their paternal branch to the proband's family. Both these patients had already been the subjects of a previous report entitled 'Familial paroxysmal ventricular tachycardia'.<sup>18</sup>

These girls were again examined and apart from the previously described episodes of syncope and vascular collapse, now admitted to dyspnoea with effort. Radiological examination showed them to have cardiac enlargement and the ECGs of both girls were similar to that of the proband. Their ECGs showed low-voltage QRS complexes with abnormal ST- and T-wave changes, and in one of the patients abnormal left axis deviation of  $-60^\circ$ , suggesting left anterior hemiblock. The echocardiogram did not reveal evidence of hypertrophic cardiomyopathy. Both were reasonably well controlled on anti-arrhythmic drugs, but were still subject to episodes of dizziness and even syncope. Exercise was again a prominent precipitant of such episodes.

### Genealogy

A family tree covering 10 generations was constructed after extensive interviews with relatives, a search through the archives and visits to cemeteries (Fig. 6). It was clearly shown that both parents were descendants of

the same French immigrant who arrived in South Africa *circa* 1700. This immigrant had 4 children, 3 sons and a daughter (gen. 2) and 3 of them married 3 children of another French immigrant, while the last son married the daughter of yet another French immigrant. Since these 3 immigrants and their children settled near each other, several intermarriages ensued. At gen. 4 first-degree cousins married in 1787 can be observed. It was possible therefore to show that the proband's paternal great grandparents (gen. 7) were related to each other.

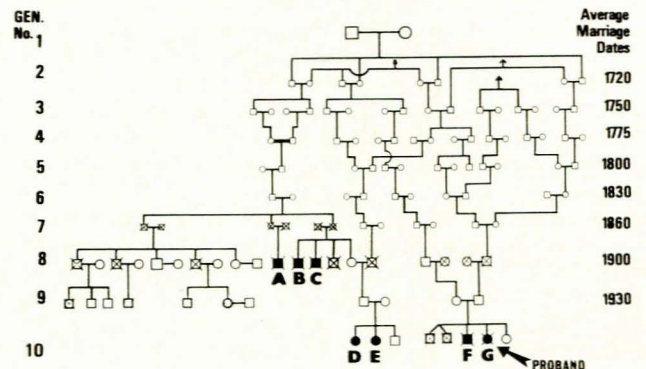


Fig. 6. Family tree extending over 10 generations.

The parents of the affected sisters (gen. 10, D and E) were also descendants of the same French settler, but only through the paternal branch (gen. 9). Paternal relatives were then sought. The paternal grandmother (gen. 8) of the affected girls (D and E) was found to be alive and could supply additional information. Her parents were not related to each other and her mother had died at about 25 years of age of an unknown cause. Two of her 3 brothers had died suddenly as teenagers (gen. 8, B and C), the one at 15 years while chasing pigs in the field, the other at 19 years while playing school rugby. The surviving brother died at 80 years of age. Her husband had died at the age of 73 and had always led a very active life. Her maternal aunt (gen. 7) lost her only son in very similar circumstances when, at the age of 22 years, he had a heart attack and died (gen. 8, A). Her maternal uncle (gen. 7) had died aged 67 years, but she did not know the cause of his death.

The only surviving son of the maternal uncle (gen. 8) reported that his late eldest brother had had 3 sons, of whom 1 had died of Hodgkin's disease at 18 years (gen. 9). His second deceased brother had an only son who, at the age of 45 years, had 2 heart attacks and was said to be suffering from hypercholesterolaemia (gen. 9). His youngest deceased brother had a son and daughter both aged about 50 years and both are said to be suffering from hypercholesterolaemia (gen. 9). The hypercholesterolaemia in these descendants has not yet been verified, since the family is widely scattered.

The paternal branch of the 2 affected sisters showed a very striking repetition of the pattern shown in that of the proband in that their paternal grandparents (gen. 8) were also related to each other. In the paternal grandmother's



family (gen. 8, A, B and C) a consanguineous marriage (gen. 4) of 2 first-degree cousins had occurred.

## DISCUSSION

The clinical picture presented by the proband and the 2 sisters (D and E) (Fig. 6) is unlike that of other cases of cardiomyopathy so far described, both with regard to the course of the disease and symptoms. Patients with congestive forms of cardiomyopathy<sup>1,5-7</sup> characteristically develop evidence of congestive cardiac failure, without life-threatening ventricular arrhythmias; so, too, do patients with obliterative types of cardiomyopathy<sup>6,7</sup> and Löffler's fibroplastic parietal endocarditis.<sup>19</sup> Literature on the features and course of idiopathic non-obstructive cardiomyopathy<sup>1,6,7,20</sup> and on hypertrophic obstructive cardiomyopathy<sup>1-3,21</sup> indicates that while sudden death and episodes of syncope are well known, this appears to be unrelated to recorded episodes of acute ventricular dysrhythmia. These forms of cardiomyopathy also do not tend to show a prolonged course with repeated episodes of syncope. Moreover, on closer examination relevant literature suggests that this type of history is to be found in the hypertrophic forms of cardiomyopathy and more frequently in the familial types of this particular condition.<sup>1-3,13,21</sup>

Another notable aspect of the symptomatology is the precipitation of syncope by exercise. This was evident in the history of the proband and of the related sisters (D and E) and the sudden death recorded in the deceased patients (B, C and F) was said to be related to exercise.

A prolongation of the QT interval was observed in the proband and directed the attention to the condition of the prolonged QT syndrome.<sup>22-26</sup> Because of the gravity of the patient's condition, and because of theoretical considerations on the imbalance of sympathetic tone and its influence in arrhythmias related to the prolonged QT<sub>c</sub> interval,<sup>15</sup> a left cervical sympathectomy was done. No definite improvement was obtained by this procedure. The prolonged QT<sub>c</sub> interval was more likely an expression of the cardiomyopathy as such with enlargement of the heart. The cardiomyopathic aspect became more evident when the heart was observed to enlarge and when signs of congestive failure, a third heart sound and a murmur indicative of mitral incompetence appeared. The ECGs of the proband and the affected sisters (D and E) (Fig. 6) also suggested myocardial pathology and were unlike the ECGs of the hypertrophic types of cardiomyopathy.<sup>3</sup>

A familial and hereditary type of congestive cardiomyopathy is not well recognised. In a description of identical twins with cardiomyopathy the authors suggest that one twin had a hypertrophic cardiomyopathy while the other may have had a congestive form of this condition.<sup>12</sup> Other authors do not attempt to draw a clear distinction between the different types when describing the familial forms, but the pathological findings published generally support the diagnosis of hypertrophic varieties as being of the familial form.<sup>13,27</sup> An African type of congestive cardiomyopathy described in 2 brothers<sup>14</sup> is more likely to be coincidental in an area where this condition is extremely prevalent.

The pathological findings in the proband's heart were quite unlike those expected in classic hypertrophic cardio-

myopathy. The attenuated muscle fibres as well as the increase in the elastic and smooth muscle elements of the endocardium indicate that cardiac dilatation had been present for a considerable time. Twenty-six blocks of the heart were examined, and in all but one the arrangement of the myofibres was very regular without any evidence of 'whorl' formation as described by Olsen.<sup>28</sup> The most likely diagnosis is that this patient has suffered from a congestive cardiomyopathy. In one block, however, two tiny foci were encountered where the hypertrophied myocardial fibres were irregularly arranged. However, if one applied the histological hypertrophic cardiomyopathy index (HHI), allotting points for each of the observed histological changes (fibrosis, bizarre nuclei, disappearing myocardial fibres, perinuclear haloes, whorls and short runs of myofibres),<sup>16</sup> a value of only 40% was obtained. This is below the figure on which definite hypertrophic cardiomyopathy can be diagnosed. However, we considered whether this case did not belong to the very rare group of hypertrophic cardiomyopathies described by Olsen<sup>28</sup>, and in which clinical obstruction had been minimal. Although asymmetrical septal hypertrophy is usually seen in these patients, it may be absent and yet show a focal distribution of abnormal myocardial fibres. There were two reasons why it was unlikely that our patient belonged to this category of patients: the HHI was low and only two tiny abnormal foci were found in a very large number of blocks examined. It was therefore concluded that this patient had suffered from congestive cardiomyopathy.

The inheritance pattern is not clear. The father and mother of the 2 affected sisters were found to be normal.<sup>19</sup> Both parents of the proband were also found to be normal. A familial relationship was, however, discovered between A-B-C, D-E and F-G. The grandfather of A-B and C (gen. 6) is a direct descendant via the male link of the eldest son of the initial immigrant. The paternal great-grandfather of D and E (gen. 7) was also married to a descendant of the same immigrant but exact relationships could not be established because of lack of data. The paternal great-grandmother of F and G (gen. 7) was a direct descendant of the youngest son of the initial immigrant.

Thirty-seven marriages, between 1720 and 1860, were studied. The surname of the initial immigrant seems to disappear entirely in the female line. Yet, in 1860 no less than 4 out of the 6 marriages contracted were between couples of whom the male or female were carriers of the surname of the initial immigrant. It is possible, therefore, that the members of this family led very isolated lives and allowed a certain amount of inbreeding to take place. If a recessive mode of inheritance is considered for the family of the proband G, then the chances for a heterozygous condition in the parents can be calculated for the mother as 1 : 512, for the father as 1 : 32. For the abnormality in D and E (gen. 10), intermarriage cannot be regarded as the possible mechanism, since the parents did not have a known common ancestor. The possibility that the female parent of this marriage did carry the gene can only be arrived at through knowledge of the incidence of the heterozygote in the general population. This is not available. The same applies to the family of A, B and C



(gen. 8). A dominant gene with variable penetration can be considered in individuals A, B, C, D and E, with a mutation in one of the parents (gen. 6). The fact of a common ancestor for the families of A, B, C, D, E, F and G may then be coincidental. A more complex mode of inheritance where more than one gene is involved cannot be ascertained with the present information. A multifactorial inheritance usually gives a clinical picture of different degrees of the condition in affected individuals. Perhaps the disease is a result of an assortive mating and its expression is regarded as a dominant new condition finding its origin in an isolated community.<sup>29</sup>

To date the only other cases of comparable description that have been brought to our attention are those described as idiopathic familial myocardiopathy in 5 generations.<sup>30</sup> The authors describe a non-hypertrophic cardiomyopathy with globular dilated left ventricles, endocardial fibro-elastosis and mitral regurgitation. This condition developed in several members of at least 3, and possibly 5, generations. However, symptoms in the 4 patients who died suddenly were minimal during life and signs of heart failure were present for only a brief time before death, if at all. Precordial murmurs, moreover, were most often detected in the first few years of life. The inheritance patterns of the disease suggest an autosomal dominant mode of inheritance.

The pathology described appears to resemble that of our patients. The clinical manifestations, however, differ: a prolonged course with recurrent frequent episodes of ventricular dysrhythmia and absence of early detection of murmurs occurs in our patients and not in theirs, but a similarity exists with regard to minimal and late onset of myocardial failure.

The fatal forms of familial cardiac arrhythmias described by others<sup>31-33</sup> do not have the pathological features of a congestive cardiomyopathy, nor could we find evidence of pathology in the conducting system such as was thought to be present in other cases.<sup>31,32</sup>

The underlying genetic defect in our patients appears to have a complex origin and to be the consequence of intermarriage and degree of inbreeding. In future it might be possible to carry out studies to define such a defect more accurately, as has been done in the case of the inbred myopathy of the B10.14.6 strain of the Syrian hamster.<sup>34</sup> This

myopathy, which presents most prominently as a congestive type of cardiomyopathy with clinical signs of cardiac failure, has been shown to be the consequence of defective transfer ribonucleic acid.<sup>35,36</sup>

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