Clinical and Pathologic Studies in the Hereditary Syndrome of a Long QT Interval, Syncopal Spells and Sudden Death*

John Phillips, M.D.** and Herbert Ichinose, M.D.†

Clinical and pathologic investigations of a family whose members suffered from a heritable syndrome of syncopal spells, sudden death, and QT interval prolongation on the electrocardiogram are reported. All members had normal hearing. The mode of inheritance appeared to be autosomal dominance. The syndrome is very similar to one first reported in 1957 by Jervell and Lange-Nielsen except in the latter disorder, nerve-deafness is present and the mode of inheritance is autosomal recessive. In the syndromes reported, attacks of syncope and sudden death are usually due to ventricular fibrillation and this is frequently triggered by physical or acute emotional stress. Of importance and as illustrated by the proposition of this study, the electrocardiogram may be normal at rest only to show the characteristic bizarre QT prolongation after exercise. Pathologic study of the heart of one of the family members who died suddenly revealed diffuse and extensive fibrosis of the conducting system along with abnormal changes in the small arterial vessels in this area. The part these lesions play in the pathogenesis of the clinical syndrome is not entirely clear. The syndrome is probably more unrecognized than rare and may explain a number of instances of “atypical seizures.” Any individual with such seizures should have an electrocardiogram, preferably after exercise, as an integral part of the diagnostic evaluation.

PROLOGUE

It is a true privilege to be given the opportunity to pay tribute to Dr. George Burch and to participate in the Festschrift in his honor. Dr. Burch is one of those rare physicians who has achieved excellence in the medical trinity of teacher, investigator and clinician. His contributions to the scientific world are boundless and their impact and meaning continue to grow with the passage of time. Dr. Burch is a man of numerous talents. We have selected the present communication in this issue for it reminded us of one of his many attributes. Although an undoubted master of the commonplace in the illnesses which beset man, through intuition and incredible perceptiveness he has uncovered and illuminated the unusual and the unrecognized. Characteristically he has analyzed and interpreted such experiments of nature and utilized these interpretations toward a fuller understanding of the more frequent disorders of man’s physiology. In this light we hope that in some small way our report of a syndrome which is probably more unrecognized than rare, will lead to a broader and more profound understanding of the mechanisms of unexpected sudden death in man.

INTRODUCTION

In 1957, Jervell and Lange-Nielsen1 described four siblings who suffered from deaf-mutism, syncopal spells and sudden death and whose electrocardiograms showed marked QT prolongation. Since then a few isolated case reports and family studies of the same syndrome with syncopal spells and sudden death attributable to cardiac arrhythmias, particularly ventricular fibrillation, have been published.2-5 These families with deaf-mutism presented an autosomal recessive pattern of inheritance.

In 1963 Romano and associates6 described a similar syndrome with QT prolongation, syncopal
attacks and sudden death, but occurring in individuals whose hearing was normal. These and subsequent family studies provided evidence that in this latter syndrome the direct familial transmission was consistent with an autosomal dominant mode of inheritance.\textsuperscript{7–10}

The present study reports the clinical findings in a family with the syndrome associated with normal hearing and the pathologic findings in one of the members of this family. The study is of importance in that it illustrates the importance of exercise electrocardiography in the diagnosis of the syndrome and further in that it presents the first detailed pathologic investigation of a heart manifesting this particular disorder.

**Clinical Findings**

The propositus was an 18-year-old Caucasian boy who was apparently in good health until age 11 when he suffered his first episode of syncope. In the next year he suffered two more such episodes. The syncopal spells were sudden in onset and lasted two to three minutes. One of the spells occurred while playing ball, but the other two occurred while swimming and almost ended fatally. He was hospitalized at another institution for evaluation of these “seizures.” The usual diagnostic evaluation was negative except for an electrocardiogram revealing bizarre T wave changes. Because of this and a soft systolic precordial murmur he underwent cardiac catheterization. This investigation gave normal results. Because of the possibility of “myocarditis” explaining the abnormal electrocardiogram, a period of prolonged restriction of physical activity was advised. He did well, syncopal spells did not recur, and the electrocardiogram by age 17 was entirely normal. Accordingly at that time he was returned to full physical activity without restriction. He continued to remain asymptomatic until age 18 when he noted the onset of sharp “stabbing” bilateral anterior chest pains of only a few seconds’ duration. These pains were seemingly of musculoskeletal origin.

Shortly after this he came under our observation for cardiac evaluation. Except for the chest pain he was asymptomatic and the remainder of his history was unrevealing. The family history was of interest in that a five-year-old brother had died suddenly of a “cardiac arrest” in a dentist's office while having a tooth extracted.

Physical examination was largely within normal limits. Blood pressure was 118/80 in both arms. The heart revealed moderate sinus arrhythmia. The cardiac impulse was normal without evidence of chamber enlargement or hypertrophy. The two components of the second sound varied normally with respiration. There was a soft ejection-type systolic murmur at the pulmonic area thought to be functional in origin. A soft variable third heart sound was audible. There was a mild pectus excavatum deformity to the chest wall, but the remainder of the physical examination, including hearing, was within normal limits.

Routine blood studies, serum electrolytes and chest x-ray films showed normal findings. Except for a QT interval at the upper limits of normal, the electrocardiogram was unremarkable (Fig 1). After exercise, a striking change occurred,


Figure 3. Cross section of the bundle of His in the membranous septal region. The lumen of the left ventricle is present on the left side. The lower left corner of the bundle shows prominent fibrosis with disarray of bundle fibers. The adjacent interventricular septal musculature is also involved (GMS x 16).

however. There was paradoxical slowing of the heart rate and the QT interval and QTc increased significantly with prominent upright T waves especially in lead V4 (Fig 1). Slight beat to beat change in the configuration of the T waves was also evident on this tracing. At other times, bizarre changes in the QT interval, ST segment and T waves occurred spontaneously at rest (Fig 2).

Electrocardiographic study of the available members of this patient's family was then undertaken with the results indicated in Table 1. It is of interest that all the family members had QT, measurements clearly abnormal or at the upper limits of normal. These findings would tend to confirm an autosomal dominance form of inheritance. The most severely affected member of the family was the three-year-old brother. Shortly after completion of the electrocardiographic study this boy died suddenly of a "cardiac arrest" while playing on the beach. His heart is the source of the pathologic study which follows.

Pathology

Gross examination of the heart showed no significant change. The fixed organ wet weight was 69.2 gm. The SA and AV nodes could be identified on cut section as slight tan and pale grey, tiny bodies (1-2 mm wide) appearing well delineated due to congestion in the adjacent tissue. The nodes and bundle of His were sectioned in the manner recommended by James.11,12 The bundle was serially sectioned from its proximal portion before penetrating the central fibrous body, through the membranous septum segment, and into the anterior superior muscular septum (5 μ sections.)

Histologically, the bundle of His showed two regional areas of dense sclerosis. One area was situated near the posterior extremity of the membranous septum. The normal triangular cut section outline of the bundle was marred by extensive alterations of the inferior left corner region involving up to 20 percent of the bundle substance and being situated in a segment measuring approximately 0.61 cm (Fig 3). In this area, the main bundle fibers were either replaced or separated by hyalinized connective tissue. The surviving fibers were in disarray (Fig 4). Some were attenuated and ended

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Figure 4. Fibrotic lesion of the bundle, higher magnification in another area. Dense connective tissue deposits have isolated the bundle fascicles and attenuated some conductive fibers. The regions of heaviest deposits in the lower part of the picture represent more complete fibrous replacement. Uninvolved bundle fibers are present in the upper edge of the picture. The left ventricle lumen is situated beyond the left edge of the picture (GMS-PTAH [Gutierrez modification], x 128).

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reticulum fiber support in an area where most of the conduction fibers had disappeared.

A second area of scarring was present in the anterior portion of the main bundle and formed a stricture around one of the left bundle branches at its point of origin. This area of scarring continued anteriorly in the bundle of His, became larger, and divided the main bundle from its branches to the left side. A segment of at least 0.5 cm was involved and replacement of up to 80 percent of cross sectional area of the main bundle was observed.

The superior ventricular septal artery situated in the apical region of the muscular interventricular septum exhibited striking changes (Fig 7). The smooth muscle of its wall was loosely arrayed and appeared hypertrophied. Elastic laminae were absent although elastic fibers were present in the adventitia. Hyalinized arterioles were present in the bundle of His.

**DISCUSSION**

We agree with Garza and associates\(^1\)\(^1\) that the syndrome herein described, even though similar in many respects, should be considered a different entity from that originally reported by Jervell and Lange-Nielson.\(^1\) This is so because of the absence of nerve deafness and the presence of an autosomal

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**Figure 5.** Fascicles of the bundle showing nodular sclerosis. A larger fascicle of the bundle is present in the left upper corner. The latter shows a minimal degree of scarring toward the center of the picture. A fascicle is present in the middle left side of the picture and shows more extensive fibrosis simulating amyloid deposits. In the lower central portion of the picture, a sclerotic nodule is present containing a few surviving conduction fibers (arrows). Pure nodular sclerotic areas are present in the lower and upper right corners. This histologic spectrum represents different stages of nodular sclerosis and indicates atrophy of preexisting fascicles of the bundle (H and E x 108).

blindly in the scar tissue, while others followed a tortuous course to the left branch fascicles. Rare fibers could be traced into tenuous connections with adjacent muscle of the interventricular septum which was also scarred. These connections were situated in the subendocardial area just deep to the left bundle branches. The left bundle was the type designated by Walls\(^1\)\(^1\) as type C and consisted of multiple branches arising from the main bundle.

The area of scarring showed two unusual stromal changes. The hyalinized fibrous tissue exhibited a noticeable nodularity which conformed in dimension and outline to the fibers and fascicles of the bundle (Fig 5). Some of these fibrous nodules contained atrophic conduction fibers. In addition, occasional fascicles of the bundle in this region exhibited a unique deposition of hyaline in between their fibers simulating amyloid. These altered fascicles, the nodules with atrophic conducting fibers, and the pure sclerotic nodules appeared to be different stages of a degenerative process referred to here as nodular sclerosis. Congo red stains were negative. The second stromal change of note in this region was a peculiar loose connective tissue which was hypocellular, resembled adipose tissue, and appeared edematous (Fig 6). Occasionally, this tissue contained conduction fibers in its periphery. These areas measured up to 1 mm in largest dimension and were believed to represent the surviving

**Figure 6.** A second stromal pattern present in the fibrotic lesion of the bundle of His. An area of loose connective tissue resembling adipose tissue is present in the central portion of the picture. Occasional surviving conduction fibers are present in its periphery (arrows). By contrast, in the left lower portion of the picture, there are areas of nodular sclerosis. The loose connective tissue is believed to represent an area of ischemic damage containing surviving reticulum fiber support of bundle tissue. The left ventricle lumen is present beyond the right edge of the picture (H and E x 140).
dominant mode of inheritance instead of the autosomal recessive pattern in the latter.

Many theories have been offered to explain the etiology and pathogenesis of hereditary arrhythmias and conduction disturbances of all types and unusual ST and T changes with QT prolongation in the absence of the common types of heart disease. These include vagal disturbances, anomalies of the conducting tissue and Purkinje fibers, central nervous system influences, asymmetrical sympathetic neural stimulation of the ventricular muscle, incapacity for normal repolarization of the myocardium due to metabolic abnormality, and hereditary pathology of the small coronary vessels. The autopsy findings in the present study would seem to indicate that pathologic changes in the conducting tissue are at least a factor underlying the syndrome. There is some similarity between this syndrome and the "late systolic click and murmur syndrome," the latter recognized for over 50 years but being reported with increasing frequency recently. Both syndromes are heritable, and both may have long QT intervals, atrial and ventricular arrhythmias, syncopal spells and sudden death. Characteristic pathologic findings in the latter disorder have been myxomatous degeneration and redundancy, particularly of the posterior leaflet of the mitral valve. The pathologic basis for the repolarization abnormality and recurrent arrhythmias, however, has remained unclear.

Of the several reports of patients with familial episodes of syncopal spells and sudden death of all varieties, to our knowledge there are only two reports in which pathologic studies of the conduction system were performed. In one of these reports, changes consistent with acute and subacute ischemic degeneration including granulation tissue and adipose tissue replacement of the SA node were noted. Greene et al interpreted the changes they found in the AV node and bundle as being congenital malformations rather than acquired lesions. They described spurious branches arising from the bundle of His and terminating blindly in the membranous septal region. Hypoplasia of the right branch and main bundle, as well as variation of the AV node architecture were also noted. No details on stromal changes were given in this report; for this reason, the possibility that the reduced size of the bundle may have been due to atrophy rather than congenital hypoplasia cannot be excluded in their two cases. The spurious branches of the main bundle which these workers described are probably related to the disarray of conduction fibers found in the area of scarring in our case. In the latter, the presence of nodular sclerosis with its apparent preservation of the outlines of the fibers and fascicles of the bundle seem to indicate atrophy of pre-existing bundle structures. Likewise, the loose areas of reticulated connective tissue resembling adipose tissue which probably represent the surviving reticulum fibers of the bundle also point to the disease as being a secondary degenerative process in our patient.

The vascular alterations in these cases are deserving of special attention. In the report of Fraser, Foggatt and James, prominent medial hypertrophy of the sinus node artery (intranodal segment) was observed. This mural change was believed to be responsible for encroachment upon the ostia of nutrient branches emerging from the artery with resultant nodal ischemia. The medial hypertrophy may represent localized segmental spasm. A second type of sinus nodal artery vascular change associated with arrhythmia and nodal damage was observed by James in the study of Dalmatians with sudden death, arrhythmia, and confluent black spots of uneven distribution in their hair. It was also noted in the nodal and systemic arteries of three unrelated patients suffering from primary pulmo-
nary hypertension. In these instances, subintimal fibrous thickening and apparent proliferating new smooth muscle in the subintima occurred. This phenomenon has been observed in organized pulmonary thromboemboli. Progressive hyperplasia of subintimal muscle with increasing degrees of atrophy of the original media have also been noted. In the latter instances, the elastic laminae merged into a common membrane and may eventually disappear. The artery at this stage may have a peculiar disarray of smooth muscle in its newly formed wall. It is readily contrasted to the compact arrangement of smooth muscle in normal tunica media. New internal elastic lamina forms rarely. An example of an artery in this stage was noted in our patient. The third pertinent observation regarding vascular supply is provided by Greene et al. On set step serial sections of the AV bundle, the nodal artery could not be identified and was believed to be absent. The survival of portions of nodal and bundle tissue indicate the presence of collateral supply. This supply is probably adequate under resting conditions, but might be unfavorably taxed during physical exercise. In summary, there is further support for James' original contention that nodal changes in these patients are ischemic in nature. Pathologic studies provide three morphologic explanations for ischemia: (1) segmental nodal arterial hypertrophy or spasm; (2) thromboembolism; (3) congenital absence of the nodal artery. It is conceivable that a genetic predisposition for vascular disease might be operative in these families but may manifest itself in either of the three morphologic lesions.

Although ischemia seems to be a significant part of the pathogenic picture, the reason for localization of vascular changes to these particular foci in the body remains unclear. Likewise, the question of how genetics controls the type and location of the disease process is as yet unexplored. In this regard, a third pathogenic consideration is that most of the morphologic changes observed up to the present are secondary in nature. With genetic alteration, the highly specialized nodal-conductive system, apparently possessing unique metabolic patterns, may be a tailor-made milieu for a metabolic aberration or a particular viral infection. With regard to viral infection, it is known that myocarditis, including the viral variety, can produce the loose adipose tissue-like connective tissue change in the nodal-conduction system which was found in James' patient and our patient. Some instances of non-specific myocarditis, possibly viral in nature, have been found to be best developed in the region of the bundle of His. The presence of fibroelastosis in one of James' patients (case 7) is also relevant. This lesion has been produced in experimental fetal infections by mumps virus.

We agree that the heritable QT prolongation syndromes are probably more unrecognized than rare and may account for a number of instances of "atypical epilepsy." Any patient presenting with attacks of "breath holding," "fainting spells," "hypoxic crises," "atypical seizures" and the like should certainly have an electrocardiogram, and it should be emphasized that if the attacks are not otherwise explained, electrocardiography should be repeated after exercise. As illustrated in the present report, the resting electrocardiogram may be normal only to become abnormal with the characteristic QT prolongation and ST-T changes after exercise. Variability of the electrocardiogram, not only from day to day, but even from beat to beat, is a frequent finding.

It would appear that the syncopal spells and sudden death are due to ventricular arrhythmias particularly ventricular fibrillation. Clinically, such episodes usually occur during periods of sudden fright or excitement or in association with physical exercise. Sensitivity to sympathomimetic agents may be responsible for precipitation of attacks. Physiologically the chief basic factor predisposing to the electrical instability would appear to be delayed ventricular repolarization with the long QT interval presenting an increase in the duration of the vulnerable period with greater susceptibility to the development of ventricular arrhythmias. In their study, Garza and associates found three mechanisms whereby ventricular arrhythmias were precipitated: 1) an increase in the systemic blood pressure with ventricular premature beats apparently induced by the pressure rise, 2) sinus tachycardia, when the impulse reached the ventricles still in a depolarized state, and 3) a ventricular premature beat occurring in the "vulnerable" phase of repolarization ("R in T syndrome"). It appears that in addition, atrial premature beats, with or without aberration in intraventricular conduction, may initiate ventricular arrhythmias or supraventricular arrhythmias which rapidly lead to ventricular arrhythmias. Minute infarctions in and around the SA node may represent the initiating source of such arrhythmias. Of further possible importance is the sinus bradycardia not infrequently observed in the syndrome. This bradycardia itself would augment the propensity to ventricular arrhythmias. The sympathetic neural and hormonal changes accompanying exercise must further increase this tendency, especially in instances of paradoxical postexercise bradycardia as the patient discussed had shown.
Prognostic indicators in the syndrome are difficult to judge because of the variability and unpredictability of the manifestations. It would seem that the longer the maximum length of the resting, and perhaps the postexercise QT interval, the poorer the prognosis. It seems clear that the syndrome becomes more benign with advancing age of the affected patient and the frequency of syncopal spells and sudden death diminishes.

Insufficient studies are available at the present time to determine ideal drug treatment in the syndrome. Diphenylhydantoin, lidocaine, diazepam, calcium and a glucose-potassium-insulin solution were all unsuccessful in preventing arrhythmias in the patient reported by Garza et al. Digitalis tended to normalize the electrocardiogram findings, but episodes of ventricular fibrillation continued to occur. Digitalis theoretically should be of value because of its ability to shorten the QT interval and in the Jervell and Lange-Nielsen syndrome (with nerve deafness) therapeutic effectiveness was demonstrated. Because of their antiarrhythmic action, quinidine and procainamide might seem of value, but their tendency to prolong the QT interval may counter any favorable therapeutic effect. Insufficient numbers of trials using these agents are available to judge their place, if any, in therapy. Theoretically, of the currently available drugs, because of its direct, quinidine-like antiarrhythmic action, its chronotropic beta-receptor blocking activity and its ability to shorten the QT, on the electrocardiogram, propranolol would appear to be an ideal drug and in truth it proved to be the only effective agent in the most recently reported patient.

Because of the association of attacks of ventricular fibrillation with acutely rising arterial blood pressure in the syndrome, theoretically the antihypertensive agents may be of value, but their worth is yet to be tested.

Further points in management of the disorder are important. Careful monitoring during dental and surgical procedures should be done. Wherever possible, the use of agents such as epinephrine (eg with local anesthetics in dental and ENT procedures) should be avoided. Physical and sudden emotional stress should be dampened when feasible. Parents and others likely to be near afflicted patients might be taught the fundamentals of cardiopulmonary resuscitation.

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From the Writings of George E. Burch

Of Painting and Therapy

To employ drugs without complete knowledge of their pharmacology is voodoo medicine and is no different from the use of herbs, spiritual dances or drums by the medicine men of primitive peoples. To use drugs by their trade names without a knowledge of the contents of the pill is deplorable and intolerable. A physician should never use a preparation or procedure unless it is fully understood; to do so is indefensible and shameful. Know the drugs and procedures and be well aware of your own ability to employ them at all time.

Proprietary preparations containing multiple drugs offer one of the greatest limitations to practice today. Most of them offer more to the practice of the witch doctor than to that of the physician. No manufacturer can mix drugs in one pill in proper proportions to fulfill precisely the needs of the patients the world over under all circumstances and at all times. The ready-mixed trade preparations meet with apparent success because it is difficult to kill a normal man; many people do not need medicine or they recover in spite of the therapy. A pill composed of a mixture of drugs has a drug ratio which can never be changed by using the same pill. The wise and thoughtful physician uses his drugs separately so that he can modify any one to meet the needs of the patient. Beware of ready-prepared mixtures when the prescription is not written by the physician. The use of a preparation containing several drugs written by an able and thoughtful physician to meet the needs of his particular patient at a particular time is “shot gun” therapy, whereas the use of a fancy pill containing several drugs mechanically stirred in a large vat by laborers plagued with non-medical thoughts, packaged in a fancy box at a fancy price with a euphonious-sounding trade name and using a fashionable prefix or suffix, is considered modern and up-to-date therapy. This is ridiculous, but the concept prevails today. The timing of each drug and each dose must be selected with thought. Rarely can a pill of mixtures prepared by others miles away meet the precise needs of any given patient; it is only tolerated. The doctor who writes his own prescription while sitting next to his patient, selecting each ingredient and dosage, is more likely to have thought more of the action and nature of the drugs than one who merely prescribes a ready-mixed pill.


Not Enough Time for An Adequate History?

There is no substitute for a good history and physical examination. These require time, a great deal of time, but are absolutely indispensable. Unfortunately, too few physicians realize this and even fewer are proficient at both. It is rather appalling when a physician believes that he does not have time to take an adequate history but can devote much time to unnecessary cardiac catheterization, ballistocardiography, vectorcardiography and other complex procedures in diagnosis and treatment. Except in emergencies, it is mandatory that a thorough history and physical examination with electrocardiogram, roentgenogram, hemogram, urinalysis and stool examinations be obtained on all cardiac patients before any therapeutic procedure is undertaken. The cardiologist is obligated to distinguish between procedures that are yet experimental and those that are established if he is to remain “pro-patient.”