Paroxysmal Ventricular Arrhythmias and Familial Sudden Death Associated with Neural Lesions in the Heart*

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A high school athlete with history of syncopal attacks died suddenly. Paroxysmal ventricular arrhythmias had been documented many times, as had at least one episode of ventricular fibrillation. A brother with similar history also had died suddenly and unexpectedly at about the same age. Except for the syncope and arrhythmias, they were both considered to be in good health. At postmortem examination, no significant extracardiac abnormalities were found, and the heart was normal on gross examination. The cardiac conduction system was the subject of special study. Focal inflammatory degeneration of small nerves and ganglia was found in various sites within the heart, including atrioventricular node, but were especially prominent in and around the sinus node. There was epicardial edema and thickening of the pericardium in that vicinity, but all of the pericardium elsewhere was normal. Some persistent fetal dispersion of the atrioventricular node was present. Ways are discussed in which these neural lesions may have contributed to the pathogenesis of paroxysmal arrhythmias and eventually sudden death. The possible etiology of the neural disease and the basis for its familial occurrence are considered.

Paroxysmal cardiac arrhythmias may or may not be symptomatic, but any form of electrical instability of the heart is fraught with some risk. Paroxysmal tachycardia in young subjects without other evi-

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dence of heart disease is generally considered to be benign in nature, as emphasized long ago by Wolff, Parkinson, and White. On the other hand, sudden unexpected death in youth is suspected by many to be due to some lethal form of cardiac arrhythmia, and even the Wolff-Parkinson-White syndrome is sometimes associated with sudden death. At postmortem examination following such deaths, the presence of virtually any anatomic abnormality within the conduction system of the heart could help shed some light on the pathogenesis of these putative ar-

rhymias. We have recently had the opportunity to do such a study after the sudden death of an otherwise healthy young man who was known to have had syncopal attacks and paroxysmal ventricular arrhythmias. This report describes the inflammatory degeneration of nerves and ganglia within the heart, including especially the sinus node, and considers their possible etiology and functional significance.

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3μg/ml, and it was decided that he was not suitably responsive to therapy with quinidine or perhaps was abnormally sensitive to it. Treatment with diphenylhydantoin sodium was begun. A graded exercise test later caused no symptoms, and the patient successfully achieved a heart rate of 180 beats per minute without cardiac irregularity of any type, although occasional premature ventricular beats were observed for several minutes after the exercise was completed. He was discharged with instructions to continue therapy with diphenylhydantoin (100 mg every six hours).

Two months later, the patient was seen as an outpatient and was found to have a level of diphenylhydantoin in the blood of 27μg/ml. There were no complaints or abnormal findings then or at a subsequent examination the next month, when another graded exercise test produced results similar to those previously obtained. The patient then returned to his usual full activity.

Three months after first being seen in consultation, the patient became light-headed while playing basketball and decided to go home. Thirty minutes later, he lost consciousness at home and was rushed to the hospital, where he was found to have ventricular tachycardia and was successfully treated with electrical cardioversion. The patient refused admission to the hospital. After several more bouts of ventricular arrhythmia, some with loss of consciousness, his therapeutic program was reassessed. Propranolol was administered (40 mg every six hours), but the patient still had another bout of ventricular tachycardia, responding to electrical cardioversion. He and his family did not wish any further investigations, and they took him home. Within the next week the patient is said to have died suddenly, but the exact circumstances are not known. A brother who had fainting spells also died suddenly at the age of 18 years while playing basketball.

An autopsy was performed, and findings were unremarkable except for the heart. The gross appearance of the heart was normal. Special examinations of the sinus node, atrioventricular node, and His bundle were conducted by methods previously published. The sinus node and atrioventricular node were normally located, and their blood supply was normal. From the anterior portion of the atrioventricular node, there was a modest amount of persistent fetal disposition of nodal fragments within the adjacent central fibrous body. Some of these fragments formed loop connections between one part of the atrioventricular node and another. Other nodal fragments were detached from the body of the atrioventricular node but were continuous with myocytes in the crest of the interventricular septum. As the His bundle coursed forward from the atrioventricular node, it remained to the right of the crest of the interventricular septum, as does the His bundle of about 15 percent of all human hearts. Such “right-sided” His bundles give rise to the left bundle branch by a more narrow stem than is usually the case and may be associated with a greater hazard for electrical instability when randomly distributed focal myocardial lesions are present. Other aspects of both left and right bundle branches in the present case were unremarkable.

There was focal inflammatory degeneration of nerves near small arteries in the ventricular myocardium; neither the arteries nor adjacent myocardium exhibited any separate inflammatory foci. Similar neural degeneration was present in and near the atrioventricular node, but the more prominent and numerous lesions were in and around sinus node (Fig 3 to 5), where ganglionitis and neuritis were extensively present. Associated with the neural lesions, there was thickening of the overlying pericardium and edema, with some inflammation of the epicardium. Deposition of fibrin or any other evidence of inflammation of the external surface of the pericardium was conspicuously absent. Along with the epicarditis and thickening of some sections of pericardium, exclusively in the vicinity of the sinus node, there was sclerosis of a few nerves within the pericardium, as if prior...
neuritis had been present and healed.

**DISCUSSION**

Some features of this case are simple and straightforward, while others are puzzling; for example, the patient was a young student and athlete in generally excellent health, except that he had recurring ventricular arrhythmias and syncope, one spell of which was fatal. A brother died just as suddenly and unexpectedly at about the same age. Clinical descriptions of such deaths in youth, some having a familial pattern, are all too familiar to any experienced cardiologist and very often have understandably been the subject of dramatic accounts in the newspapers. On the other hand, it is not clear why some otherwise healthy young people should fall victim to such recurrent arrhythmias or why there should be a familial pattern. While there was an impressive amount of neural pathologic abnormalities in and around the cardiac conduction system in the present case, the etiology of such abnormalities is uncertain, and its relevance to the familial sudden death is equally obscure. Each of these questions merits separate discussion.

**Ventricular Arrhythmias**

There seems to be little doubt that the spells of fainting were due to ventricular arrhythmias and that the fatal episode was one which did not terminate before death. Ventricular fibrillation was found to be present on at least one occasion. While this could have begun de novo, it seems more likely that

![Figure 2. Twelve-lead ECG at top was recorded on initial examination, and one at bottom was recorded three months later. Slight ST-segment elevation in first record was not considered significant, but in later tracing, there is deeper T-wave inversion over much of precordium. Paper speed was 25 mm/sec, with standardization of 10 mm/mV.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21153/ on 06/27/2017)
a prolonged bout of tachycardia ended in fibrillation, but that tachycardia stopped prior to fibrillation at other times. In several observed episodes of tachycardia, the QRS complexes were broad, and P waves could be identified dissociated from them (Fig 1), fulfilling the usual criteria to diagnose ventricular tachycardia; however, most of the deformity of the QRS complex was in its initial inscription with a more normal terminal portion, resembling ventricular preexcitation complexes. Furthermore, the rate, which was often found to be over 200 beats per minute, is somewhat excessive for true ventricular tachycardia. An alternative electrocardiographic diagnosis could be supraventricular (possibly atrioventricular junctional) tachycardia with aberrant ventricular conduction and atrioventricular dissociation. No delta wave was seen during sinus rhythm, nor was there any appreciable shortening of the P-R interval, but it is well known that some forms of Wolff-Parkinson-White syndrome are intermittent in nature. The inability to precipitate such an episode during electrophysiologic studies leaves us with no definitive answer to this question. Whatever the exact mechanism may have been, the rate of ventricular contraction was clearly very rapid, the patient was found to be hypotensive during such episodes, and there can therefore be no reasonable doubt that the bouts of unconsciousness were caused by the arrhythmia.

Two special factors may have contributed to the pathogenesis of the arrhythmias. These are the sinus bradycardia (Fig 2) and the fetal dispersion of the atrioventricular node. Slower heart rates are known to be associated with predisposition to premature beats and ectopic rhythms. There was sufficient abnormality in and around the sinus node to suspect that its pacemaking ability was faulty. If some of the perinodal neural degeneration involved sympathetic nerves, this would be still further reason to expect slower sinus rhythm; 8 But whatever its mechanism may have been, sinus bradycardia was present, even before the administration of propranolol. Fragmentation of the atrioventricular node could facilitate the appearance of atrioventricular junctional rhythms in at least two ways. First, the loop connections and other structural separations of components

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**Figure 3.** Edema, focal hemorrhage, and inflammation were abundant in and around neural elements in vicinity of sinus node. A (top), One nerve is marked with three arrows; boxed area is shown at higher magnification in B (bottom), where two smaller nerves are indicated with arrows (Goldner trichrome stain).
of the atrioventricular node form a highly suitable anatomic substrate for longitudinal dissociation of conduction, which would favor reentry and, under appropriate conditions, the production of reentrant tachycardia. Secondly, atrioventricular nodal fragments isolated from the node itself but attached to myocytes of the interventricular septum offer anatomic and physiologic conditions conducive to the emergence of parasystolic rhythm. Thus, the combination of slowing of the sinus node with circumstances favoring the emergence of atrioventricular junctional rhythm (with or without ventricular aberration) offers at least one highly plausible explanation for paroxysmal arrhythmias. There is still another possible source for such arrhythmias, which is dependent on altered ventricular repolarization, but that will be discussed subsequently together with a consideration of why the T waves became inverted.

**T-Wave Inversion**

Some time during the month between the first and second examinations of this patient, deep T-wave inversion appeared in most of his precordial leads, and these persisted for the rest of his life. Except during tachycardia, the QRS complexes did not change. During life, there was no clinical or other evidence to support the diagnosis of pericarditis, myocarditis, or myocardial ischemia, although some ischemia was undoubtedly present transiently for a short period after some of the bouts of tachycardia. At autopsy the coronary arteries and all of the ventricular pericardium were normal, and there was no evidence of myocarditis independent of the neural disease.

Central (brain or autonomic ganglia) distortion of adrenergic neural control of the heart can cause gross distortion of T-wave polarity and Q-T duration. In a recent study of several patients who died with the long Q-T syndrome, it was found that ganglionitis and neural degeneration were prominent within the hearts of all of the patients studied. It is simple to visualize how adrenergic neural influence could become asymmetric due to
focal neural disease within the heart, at least as readily as because of some central neural disorganization. In the present case, there were neural lesions scattered in the ventricular myocardium that were entirely suitable to account for the observed alteration of repolarization. Since the extent of neural abnormality was greater in and around the sinus node, including a number of lesions with a histologic appearance suggesting that they were old, the absence of T-wave inversion in the earlier ECGs may mean that the ventricular neural lesions were more recent.

Altered ventricular repolarization, especially if it was intermittently prolonged, could also facilitate the development of ventricular arrhythmias, since any premature beat would have a greater chance of falling within the ventricular vulnerable period. It is this combination which is thought to be responsible for the recurring ventricular arrhythmias characteristic of patients who have the long Q-T syndromes, with or without deafness. In our patient, we found no example of such prolongation of ventricular repolarization, but it is known that even in patients with long Q-T syndromes, the duration of the Q-T interval is highly variable and is at times even within normal limits. In other words, the presence of marked T-wave inversion in our patient certainly indicated abnormal ventricular repolarization, which may intermittently have become prolonged. As a final point, there was distinct epicarditis in and around the sinus node, but the pericardium itself, while thickened, exhibited no evidence of actual pericarditis. Since all of the pericardium over the ventricular myocardium was entirely normal, it seems unlikely that the focal epicarditis near the sinus node could have accounted for the precordial T-wave inversion. We believe that all of the epicarditis was simply a part of the active neuritis, since the epicarditis was found only in association with that neuritis.

Cardiac Ganglionitis and Neuropathy

All stages of neural inflammation and repair were present, including edema with focal hemorrhage and leukocyte infiltration at the one extreme, and
dense old scarring of some small nerves at the other. In view of the clinical history, we suspect that the neural disease was intermittent or that it waxed and waned in severity. Whatever the etiology, it is probable that the process was one of some duration, at least many months and perhaps several years.

Two major etiologic possibilities, not exclusive of each other, are some form of heritable or metabolic neural degeneration and the presence of some chronic infection. There was no clinical or postmortem evidence of extracardiac neural disease, although admittedly its presence in some organs could easily escape detection unless especially sought. Furthermore, there was no skeletal myopathy or osseous malformation or other clinical stig mata of the type associated with some of the more familiar forms of heritable neural diseases. In previous cases exhibiting similar neural lesions,15 it has been argued that herpes simplex and herpes varicella/zoster are among the more attractive etiologic suspicions. Both infections are known to be capable of lying dormant for many years, only to be activated by some form of physical or other stress or to reactivate without apparent cause. Of these two forms of herpes, the virus of herpes varicella/zoster is particularly known to affect single autonomic ganglia, particularly within the thorax, and one may anticipate that by random chance the cardiac ganglia would be vulnerable. Absence of oral or genital lesions of the type caused by herpes simplex, or of either chicken pox or shingles, could be cited as evidence against a herpetic etiology; however, it is possible to have ocular lesions or cerebral lesions or trigeminal ganglionitis without associated cutaneous evidence of herpetic infection. Precise determination of etiology clearly requires much further investigation.

Familial Sudden Death

The patient and his brother both died suddenly and unexpectedly following a series of observed syncopal attacks extending over long periods of time. Both probably died of some form of arrhythmia. We have no information about the exact clinical course of the brother nor any postmortem findings. If it is presumed that both brothers had some form of cardiac ganglionitis and neural degeneration, as has been demonstrated in other cases of familial sudden death,12 then it is important to consider the etiologic diagnosis as just discussed. Certainly some form of heritable neuropathy could be familial in nature, but the absence of any supporting clinical evidence in either brother weakens the case. It seems doubtful that a heritable neural degenerative process which affected the heart would not have had some extracardiac manifestation recognizable in at least one brother.

A chronic viral infection, especially of the herpes varicella/zoster type, would characteristically have a familial occurrence. In fact, it is the familial aggregation of such infections, cycling through older and younger members of the same family alternately as chicken pox and then shingles and so on, that is thought to account for many aspects of the epidemiologic features of both herpes varicella and shingles.12 This would not preclude some form of heritable predisposition to infection with the virus of herpes varicella/zoster nor some form of special susceptibility by neural elements within the heart as a locus minoris resistentiae. Nevertheless, whether there was any heritable predisposition or not, we suggest that a communicable chronic viral infection is the most plausible explanation for the familial occurrence of sudden death in the present case.

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