CLINICOPATHOLOGIC CORRELATIONS

De Subitaneis Mortibus

XXVI. Fatal Electrical Instability of the Heart Associated with Benign Congenital Polycystic Tumor of the Atrioventricular Node

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SUMMARY Benign congenital polycystic tumors of the atrioventricular (A-V) node are an unusual but not very rare cause of heart block. Two such cases are presented and discussed in conjunction with the reported experience of others. The tumor is always within and only very near the A-V node, seldom involves more than the proximal end of the His bundle, and has not been reported to occur in the sinus node. Although sudden death has been reported in conjunction with these tumors, a surprising number of other patients have lived to old age and died of causes unrelated to the A-V nodal tumor. As a corollary it is important to consider a diagnosis of A-V nodal tumor in any patient of any age who presents with otherwise unexplained heart block or syncope. From accumulated experience it appears that such patients do not tolerate electronic pacing safely and some possible explanations for this are discussed. Escape rhythm in all reported cases has been characterized by QRS complexes which are narrow and a ventricular rate which is from half to two-thirds of the sinus rate. Reasons why an A-V junctional rhythm which is 66% of sinus rate may be especially stable are discussed.

FOR OVER HALF A CENTURY there has been continuing medical interest in a form of heart block associated with an unusual tumor of the atrioventricular (A-V) node.1,2 While sudden death has been attributed to such tumors,3-10 that is not always true. On the contrary, one of the impressive clinical features of such cases has been their longevity, a surprising number having been 70 or 80 years old.11-13 Since most believe that such tumors are of congenital origin, one must deduce that they either lie functionally dormant in the heart for a very long time, or that they do not themselves "cause" sudden death. A more logical concept would ascribe a contributory role to such tumors in the pathogenesis of syncopal attacks and sometimes sudden death, but would require additional factors (which may be of varied nature) to culminate in fatal electrical instability. The purpose of this report is to describe two cases of heart block due to benign congenital polycystic tumor of the A-V node, and to consider the embryological and physiological significance of such tumors.

Case Reports

Case 1

A 65-year-old woman was admitted to the hospital because of weakness and chest pain radiating to the left arm. She gave a history of two syncopal episodes, occurring four and one years previously, and had been known to have incomplete heart block for about one year. At the time of admission she was slightly cyanotic, obese and was found to have varying degrees of A-V block on an electrocardiogram (fig. 1). A bipolar electrode was inserted through the jugular vein into the right ventricle and pacing was begun at a rate of about 70/min. There was sudden spontaneous arrest of the heart and respiration from which the patient could not be resuscitated.

At necropsy examination the important abnormalities were in the heart, which exhibited moderate left ventricular hypertrophy. The cardiac valves and the coronary arteries were not significantly abnormal. Just above the septal attachment of the tricuspid valve in the interatrial septum there was a small irregular tumor. It was polycystic and directly involved the A-V node (figs. 2-4). Walls of the cysts were lined by single and multiple layers of epithelial cells. Near the cysts there were foci of solid tumor comprised of cells resembling some of those lining the cysts. Although tumor replaced most of the A-V node and could be seen in the very proximal part of the His bundle, the remainder of the His bundle and its branches were normal. Both the sinus node and its arterial supply were normal, as was the artery of the A-V node.

Case 2

A 48-year-old woman was admitted to the hospital for treatment of a widely metastatic hypernephroma. During her hospitalization she was found to have heart block (fig. 5), which had probably been present for many years. Her heart rate and cardiac function were stable and not associated with syncope or recognized arrhythmias. Death was due to progressive deterioration from the hypernephroma rather than cardiac disease. Some details of this case have been reported previously.14-16 Unpublished observations to be presented here are for the sake of comparison to case 1 and similar cases.

At necropsy examination of the heart the sinus node and most of the His bundle and its branches were normal (fig. 6). The A-V node was virtually replaced by a benign polycystic tumor (figs. 7-9), not hypernephroma as first interpreted.14

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Recognizable elements of A-V node were dispersed throughout the tumor (fig. 9). In the most proximal portion of the His bundle, where it joined the A-V node, there was tumor in about one half of the cross sectional area (figs. 10 and 11) but the remainder of the His bundle and its branches were free of this tumor. Fragments of A-V nodal cells were dispersed in the central fibrous body and contained varied mixes of tumor cells with them (figs. 8, 10, 12). Branches of the A-V node artery within the node were variably narrowed in their lumens (fig. 13). At its posterior margin the tumor continued for about 1 cm into the Eustachian ridge (fig. 14), and for a comparable distance up above the A-V node into the interatrial septum. There was no tumor in the crest of interventricular septum. Portions of the tumor contained solid

Figure 1. ECG of case 1. Black dots mark conducted sinus beats and white dots ones which are not conducted in lead II, but similar marking of P waves in V1 illustrates dissociation of atrial and ventricular beats. QRS configuration is narrow and consistent in each lead, although ventricular cycle length varies from short (asterisk in V5) to long (asterisk in aVF).

Figure 2. Tumor in and above the A-V node of case 1 is shown. Arrows in A mark the A-V node and the boxed area is that magnified in B. All photomicrographs are from sections prepared with Goldner trichrome stain. MV is mitral valve, LV left ventricle, RA right atrium and TV tricuspid valve.
aggregations of cells as well as polycystic structures, some cysts containing amorphous Schiff-positive material. There were numerous profiles of tubules as well as cysts. In general the tumor was predominantly cystic in its anterior portion (toward the His bundle) and contained more numerous solid nests of cells toward its posterior portion (toward the Eustachian ridge). Concentrating attention on only one region of the tumor could thus give a false impression about the relative prevalence of cystic compared to solid lesions.

Discussion

One of many puzzles about benign tumors of the A-V node is why they often remain functionally dormant for so long. Although some reported cases died early in life (including the five-year-old child studied by Mönckeberg and Armstrong,1,2) an impressive number have been seventy or eighty years old. Furthermore, some of the older subjects clearly died of noncardiac causes, as did our second case. Bharati and her colleagues3 have commented on the impressive electrophysiological stability observed in many of these patients. It may thus be almost as justifiable to say that benign tumors of the A-V node assure longevity as to say that they "cause" sudden death, although there is no question that some patients having such tumors have died suddenly and unexpectedly.2,3 Given this wide range of ages at which symptoms first appear and diagnosis is initially made, it becomes essential to think of an A-V nodal tumor in any patient of any age who presents with unexplained heart block or syncope.

Another puzzle concerns the embryogenesis of these benign A-V nodal tumors. It is generally agreed that they are congenital in origin and epithelial in nature. Evidence supporting the opinion that they are mesotheliomas has been summarized by Fine and Morales.10 Evidence that they are tumors of endodermal origin has been summarized by Sopher and Spitz,8 who do not consider them to be mesotheliomas. Others have described them to be lymphatics or blood vessels or hamartomas or epithelial in-

**Figure 3.** In case 1 tumor tended to spare cells bypassing the A-V node (BPT in A), but was scattered throughout the midportion of the A-V node (B).
FIGURE 4. In the eustachian ridge (ER) of case 1 directly adjacent to the A-V node there were cysts and tubules (A) similar to those in the node. Multicellular solid tumor masses were interspersed with cysts and tubular profiles (B). A variety of secretory debris was present in the cysts and tubules.

FIGURE 5. ECG of case 2 illustrates complete A-V dissociation, narrow QRS complexes, and a ventricular rate which is 66% of the sinus rate.
clusion cysts. We agree with Bharati and her colleagues who suggested that because of the divergent opinions as to cellular origin, these are best termed simply tumors of the A-V node. Since they seem to be benign and nearly always polycystic, these are probably suitable additional descriptive adjectives.

There is great variability both in the symptoms and in the degree of heart block observed in patients with an A-V nodal tumor. Some present with syncope or die suddenly and unexpectedly, while others deny symptoms at all during very long lives. Given this variability of clinical expression by A-V nodal tumors, one may surmise that their true incidence is greater than is generally appreciated. Unless histological examination of the A-V node and His bundle is performed, it is impossible to say whether an A-V nodal tumor was or was not present in any patient dying with any degree of heart block, whatever other cardiac or noncardiac diseases there were.

Heterotopic tissue sometimes found in the heart includes thyroid and kidney. Hypernephroma not only can invade the heart, but there is an interesting association between hypernephroma and the variety of polycystic and angiomatous lesions (in brain, kidney, pancreas, liver, lung and retinae) seen in von Hippel-Lindau disease. It is possible that our second case represents an analogous coinciding of hypernephroma with a polycystic tumor of the heart; however, she had no other stigmata of von Hippel-Lindau disease.

Small pieces of tumor (including tubules and cysts) were dispersed together with A-V nodal cells within the central fibrous body of case 2 (figs. 8, 10, and 12). Similarly dispersed A-V nodal fragments without tumor have been identified in some victims of sudden death and are believed to represent persistent fetal dispersion of the A-V node within the central fibrous body. If that is true, then accompaniment of tumor pieces with these A-V nodal fragments supports the concept of a common embryological development, both the tumor and the primitive A-V node migrating inward perhaps with the dorsal endocardial cushion.

Extent of the tumor within and around the A-V node has

**Figure 6.** The sinus node (three arrows) and most of the His bundle (similarly marked) were both normal in case 2.
FIGURE 7. Extent of the tumor in and near the A-V node of case 2 is illustrated with sections from the posterior (A), middle (B) and anterior (C) portions of the node. The sections were made about 2 mm apart. Arrows mark the general outline of the A-V node.

FIGURE 8. A-V nodal shape is preserved despite extensive tumor (case 2). Area boxed in A is shown at higher magnification in B. Arrows in A point to fragments of A-V node with accompanying tumor dispersed within the central fibrous body (CFB).
Figure 9. Typical A-V nodal fibers and cells can be identified throughout tumor tissue in A (case 2). Variation of the number of cell layers and type of cells lining cysts and tubules is shown in B.

varied in different reported cases, but there is a remarkable uniformity when one considers all such cases. The tumor is always in and immediately around the A-V node, extends only short distances (a centimeter or so) up into the interatrial septum or back into the Eustachian ridge, virtually never extends more than a very short distance into the His bundle (most of which is conspicuously normal), does not extend into either the tricuspid or mitral valve, and has not been reported in the subjacent interventricular septum. The tumor is not only in and around the A-V node, it is itself shaped like the A-V node (figs. 2, 7, 8). While this shape may be attributable in part to guidance by collagen planes and existing A-V nodal cells and fibers, one must also consider whether the tumor originates within and is actually an integral part of the A-V node rather than necessarily a heterotopic intruder. If it originates from some cell of the original A-V node, however, it is difficult to explain its propensity to form tubules, cysts and other gland-like structures which appear to have at least intermittent secretory function. Except for its neural elements, no local secretory or glandular function is known to be present within the A-V node, and these tumors do not appear to be neurosecretory structures.

Whatever the original source of these tubules and cysts within the A-V node, their intermittent secretory function may account for either progression or waning degrees of heart block. There have been no reports of mitotic activity within such tumors and we saw none; however, secretory activity could cause local enlargement of the tumor, particularly if the secretions could not readily be eliminated. In this regard, the tumors do not appear to communicate with either the endocardium or the epicardium by channels, itself an interesting avoidance and one possibly of embryological significance. If tumor enlargement and therefore A-V nodal compression or further distortion is truly due to intermittent secretory activity, then one must ask what the control of this activity may be. The distinct predominance of such tumors among women rather than men may be significant, as may be the occurrence of initial symptoms or first clinical diagnosis of heart block during pregnancy. However, this would not explain the cases occurring among men unless some other hormonal perturbation were to be invoked. Furthermore, the first detection of heart block during pregnancy in some women may be simply because that was their first cardiac examination.

Equally intriguing is the conspicuous sparing of the His bundle except at its most proximal margin where it connects with the A-V node. This may be best ascribed to a separate origin of the A-V node and the His bundle within the human embryo, the A-V node being a left counterpart of the sinus node and both being epicardial in location originally, while the His bundle originates almost in situ at the crest of the interventricular septum. A number of congenital anomalies and other abnormalities of the A-V junctional region support this concept of separate origins of the A-V node and His bundle. The reason that benign congenital polycystic
tumors of the A-V node spare the His bundle may be because it normally originated separately from the A-V node. If the sinus node and A-V node are paired primordial structures originally located at the junction of right and left superior cardinal veins, respectively, with the sinus venosus, then it is unclear why a congenital polycystic tumor should involve only one of these two nodes. Although the sinus node may rarely include hamartomatous tissue,28 we are not aware of tumors such as the ones in this report having been found in the sinus node. One may say that the heart block from an A-V nodal tumor is a more conspicuous clinical finding which leads to careful examination of the appropriate area. But in such cases when the sinus node has also been examined, as in both of our patients and some others,3, 12, 24 it was free of such tumor. Explanation of why the A-V node is involved and the sinus is not may give us valuable insight into their embryological development as well as the pathogenesis of the tumor itself.

Nearly all reported examples of heart block due to benign tumors of the A-V node have been associated with narrow QRS complexes in the electrocardiogram. Rates have ranged from 50 to 70% of documented sinus rates in cases with published electrocardiograms,3, 5-7, 9, 11, 12, 24 and an impressive number of ventricular rates have been about 66% of the sinus rate. In fact, the case under direct medical observation for the longest period of time (a patient of Paul Dudley White) had a ventricular rate of 50 during the documented sinus rate of 75/min or exactly 66%.11 The remarkably stable cardiological course of this woman, who died of dementia at the age of 80 but was known to have heart block for 68 years, may in part be attributable to factors associated with the ventricular rate being 66% of the sinus rate. Our second case also had stable heart block and the ventricular rate averaged about 66% of the sinus rate (fig. 5). From experimental observations in the dog, two types of A-V junctional escape rhythms have been defined which bear a precise mathematical relationship to the normal sinus rate.

Figure 10. The upper half of the proximal His bundle of case 2 contained tumor, but the lower half here and all the more distal His bundle (see fig. 6) were free of tumor. Open arrows mark tumor and black arrows the spared His bundle, both within the His bundle as well as the dispersed fragments (box in A, shown at higher magnification in B) within the central fibrous body.
Figure 11. The half of His bundle cross section above the arrows in A is filled with tumor (case 2), and the boxed area is shown in more detail in B.

Figure 12. Both the A-V node (AVN) and its dispersed fragments within the central fibrous body (CFB) contained tumor in case 2. Area circled in A is shown in more detail in B.
The first of these26 emerges following selective pharmacological suppression of the sinus node and has a rate of 66% of the original sinus rate. The second type is slower (22% of sinus rate) and emerges after selective pharmacological production of complete A-V block.26 For long periods of time, the former type of A-V junctional rhythm is more stable than the latter. Further experimental observations suggest that both forms of A-V junctional escape rhythm originate in P cells located near the junction of the A-V node and His bundle, but that the faster (and more stable) rate may be associated with a larger functional population of such cells.27 These experimental observations fit well with the probable location of the origin of the escape rhythm in patients with heart block due to benign tumors of the A-V node.28 In the light of published descriptions of the exact histological extent of the A-V nodal tumors, the escape A-V junctional rhythms must originate at or near the junction of A-V node and His bundle, and the rate would be a smaller percentage (50% or so) of sinus rate when few P cells remained and would be a larger percentage (up to 66%) when more such cells were intact in that area. For such calculations to have merit it is essential to know, of course, that the sinus node itself was normal, as in both our patients.

Given stability of the A-V junctional escape rhythm in many reported cases and for impressive lengths of time in some of them, what of the factors leading to instability or to its ultimate expression in sudden unexpected death? Growth of the tumor size by an increase in retained secretions has already been mentioned as one possible change of functional significance. On the other hand, there is nothing which prevents the ordinary progression of concomitant cardiac disease in subjects with a tumor of the A-V node, so that coronary disease or myocarditis may coexist and combine with the effects of the A-V node tumor in a lethal fashion. Narrowing of small local arteries in or near the tumor (fig. 13) may be a slowly progressive basis for focal ischemia and electrical instability of the A-V node. In view of the histological organization and location of these tumors of the A-V

Figure 13. A narrowed branch of the A-V node artery (box in A) is shown in more detail in B from case 2.
node it is surprising that paroxysmal tachycardias of a re-entrant nature are not a frequent clinical problem, but they do not seem to be. Changes in ventricular repolarization (QT interval variation) may be an especially unfavorable change predisposing to ventricular fibrillation, as has been documented in one case.5

One final concern is the unsatisfactory and sometimes catastrophic response to electronic pacing in patients with heart block due to benign tumor of the A-V node. Sudden death occurred just after the beginning of pacing in our case 1 and has been reported after either endocardial or epicardial pacing by others as well.5, 6, 12, 24, 29 There may be a special hazard associated with electronic pacing (or even diagnostic electrophysiological studies) in patients with heart block due to benign tumors of the A-V node, although one might expect almost the opposite. Contrary to the suggestion that a clinical diagnosis of heart block due to tumor of the A-V node is not to be expected,11 others have stressed that such a possibility should regularly be included in the differential diagnosis.5 If there is a special hazard in either diagnostic or therapeutic pacing of such patients, consideration of the possible presence of an A-V nodal tumor becomes even more important clinically.

Although surgical resection of an A-V nodal tumor has been suggested,5 we do not see how it could be done without destroying all of the A-V node and some of the immediately adjacent structures. The inevitable consequence would be the same complete heart block which the tumor itself causes. However, if electronic pacing is required but carries the hazard which it presently seems to do, the intentional surgical production of heart block followed by permanent pacing merits some consideration as a means of securing electrical stability.

Explanations for danger from electronic pacing in these patients could include the intermittent persistence of some A-V conduction antegrade (many cases have varying degrees of such conduction), with arrival of either a conducted sinus beat or a paced electronic one during the ventricular
vulnerable period, leading to ventricular fibrillation. Furthermore, the facility of retrograde conduction from paced ventricular beats may vary, so that sinus rhythm would not be regularly overdriven. If the focus from which the spontaneous A-V junctional rhythm originates has entrance block, functioning more or less as a parasympathetic focus, then there may be chaotic competition and disorganization of electrical stability during paced electronic ventricular rhythms. Whether any of these speculations is correct or not, it is necessary to be aware that electronic pacing is fraught with some hazard in patients with heart block due to benign tumors of the A-V node. In the absence of syncopal attacks or similar warnings of intermittent electrical instability in such patients, many of them live well for a very long time on their own.

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