Histopathology of the Conduction System in the Sudden Infant Death Syndrome

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SUMMARY The cause of the sudden infant death syndrome (SIDS, crib death, or cot death) is unknown. Current hypotheses include liability of heart rate and/or rhythm as a pathogenetic factor. The conduction system of 50 infants coming to autopsy were examined by serial sections; the infants were from newborn to two years of age. Twenty-six were SIDS deaths and 24 were explained deaths (ED). The frequency of histologic abnormalities of the specialized tissue was almost identical in both groups of infants. Hemorrhage in or around different parts of the conduction system was present in 27% SIDS and 29% ED. There was no evidence of cell death or degeneration of conduction fibers, nor obstructive lesions of the atrioventricular (A-V) arteries. Apparent moulding of A-V node and His bundle was a universal finding in both SIDS and ED, and consisted of irregular interdigitation of A-V node and His bundle fibers with the myxoid central fibrous body (CFB). Isolated bundles of conduction fibers residing in CFB and membranous ventricular septum were seen in two SIDS, but no direct contacts between these fibers and the working myocardium could be identified in serial sections in either case. Without corroborating ante-mortem electrophysiologic data, the functional significance of morphologic findings in the conduction system of SIDS must remain conjectural.

Methods

The hearts from autopsies on 50 infants, 26 SIDS and 24 ED, were used for this study. The SIDS group were infants referred to the Harris County Medical Examiner's Office because they had died suddenly and unexpectedly. Their deaths remained unexplained after a complete autopsy including detailed histologic, toxicologic and postmortem microbiologic studies. The ED group were infants who died at the Texas Children's Hospital of various causes (explained death, ED).

Each year in the United States about 10,000 infants die without a detectable preceding illness, and in nearly all of them the autopsy fails to show an adequate cause of death.1 With the general decline of infant mortality, the sudden infant death syndrome (SIDS, crib death or cot death) stands out as the leading cause of death during the first year of life. Parental anguish in such tragedies is often heightened by an unfounded suspicion of negligence or self-reproach.2

Although a number of important social and biological characteristics of the high risk infant SIDS candidate have been identified, the ultimate mechanism responsible for SIDS is unknown. Current hypotheses include instability or sudden interruption of some basic cardiac and/or respiratory physiologic function.3, 4 Some investigators have attributed SIDS to certain morphologic abnormalities of the cardiac conduction system. James,5 Anderson et al.,6 and Ferris6 describe cell death, degeneration and fibrosis of the atrioventricular (A-V) node and His bundle, but the validity of these findings has been questioned by other investigators.4, 7 More data are needed to provide a balance of opinions, and for this reason, we undertook a study to compare the histopathology of the conduction system in comparable numbers of SIDS victims and infants in the same age group who had died from other known causes (explained death, ED).

Results

There were 16 male and 10 female infants in the SIDS group, consisting of 9 whites, 12 blacks and 5 Latin Americans. The ED group had 14 male and 10 female infants, and consisted of 12 whites, 8 blacks and 4 Latin Americans. The age range of SIDS and ED infants were comparable; 20 of 26 SIDS infants were between one month and one year of age, and 22 of 24 ED infants were one year or younger.

All hearts were formalin-fixed, and the initial examination at autopsy had excluded congenital cardiac anomalies. Tissue blocks containing the sinoatrial node (SAN) and the A-V conduction system were removed, paraffin embedded, and serially sectioned at 5–7 μ thickness.8 Every tenth and the adjacent sections from each block were stained with hematoxylin-eosin and Movat's pentachrome. All intervening sections were kept and processed as deemed necessary for additional hematoxylin-eosin stained sections or other special stains. For each heart, the average number of histologic sections examined was about 150–200. The sections were number-coded and examined without knowledge of the infant's identity. Only after the histologic assessment of the conduction system had been completed were the pathologic findings matched with the corresponding case records.
spaces, was present in or around different parts of the conduction system in seven infants in each group (27% of SIDS and 29% of ED). The most common sites of hemorrhage were approaches to the A-V node, the A-V node, and the left bundle branch (fig. 4). However, multiple petechiae of the epicardium and subendocardium were seen in about 50% of both SIDS and ED; most of these infants also had petechiae in the pleura, thymus and mediastinal lymph nodes.

The central fibrous body (CFB) which provides skeletal support for A-V node and His bundle, was composed of a loosely woven connective tissue in all infants, being more myxoid and less collagenous than its counterpart in adults. Special stains showed that the CFB contained large quantities of acid mucopolysaccharides in all hearts, but no true cartilage was found in any. Constant reshaping of the A-V node and His bundle by CFB was seen in the hearts of all SIDS and ED infants, differing between individual infants only in degree and not in its general morphologic character. This apparent moulding process resulted from irregular interdigitation of CFB and conduction fibers on the left side of the A-V node and His bundle, and not true replacement fibrosis (fig. 5). No cell death or degeneration as described by James, Anderson et al., and Ferris could be identified, nor was there evidence of an inflammatory response and macrophage infiltration. Graphically, the A-V node and His bundle consisted of archipelagoes of specialized fibers in the sea of CFB astride the crest of the muscular ventricular septum (figs. 2, 3 and 5). This moulding process was most evident during the first year of life, and appeared complete by the age of two years when the A-V node and His bundle assumed the adult configurations and the CFB became more compact and collagenized.

The myxoid character of the CFB appeared to be a hallmark of infantile connective tissue in general. The same histologic feature was also seen in all infants' heart valves.

In two SIDS infants, small bundles of conduction fibers appeared to have been left behind in the membranous ventricular septum, located at some distance away from the main mass of His bundle (fig. 6). However, direct contacts between these lost fibers and atrial or ventricular myocardium could not be identified in serial sections. We also found no evidence of accessory atrioventricular tracts described by Anderson et al. nor focal myocarditis in any of the hearts examined.

A comparison of our findings and those of others is summarized in table 2.
CONDUCTION SYSTEM IN SUDDEN INFANT DEATH/Lie et al.

Discussion

Despite the growing interest of the laity, government agencies and the medical community at large, the riddle of SIDS remains unsolved. The pathologic findings in autopsied cases of SIDS are almost without exception minimal in the extreme. It seems improbable that a single etiologic agent or pathogenetic mechanism is responsible for SIDS. Some current hypotheses implicate instability or sudden interruption of some basic cardiopulmonary physiologic function as the final pathogenetic pathway in the syndrome. Pertinent to this issue are recent reports of observed apneic episodes and a fortuitous antemortem documentation of labile cardiac habituation to auditory stimuli in infants who subsequently died of SIDS. The supposition was that unstable or abnormal autonomic discharge could account for respiratory and/or cardiac arrest.

The theory that a lethal cardiac arrhythmia or heart block may be related to structural abnormalities of the conduction system in SIDS is attractive. James first explored this possibility and described moulting of the A-V node and His bundle. He identified areas of cell death, degeneration, macrophage infiltration and replacement fibrosis. Although similar changes were also present in control (non-SIDS) infants, he postulated that lethal arrhythmias or conduction disturbances due to the changes described may be responsible for SIDS. James' theory was later briefly restated by Anderson et al. and Ferris. These authors invoked ischemia as the most likely cause of conduction cell degeneration and fibrosis. James reported significant luminal narrowing of the A-V artery in about one-third of infants (both SIDS and controls) as did Anderson et al. in their SIDS infants.

Two more recent reports by Valdes-Dapena et al. and Anderson et al. disputed James' findings and the interpretation of his histologic observations, as did our study. We found no evidence of cell death, degeneration and fibrosis of the conduction system in the hearts of any of the 26 SIDS and 24 ED, nor a single example of obstructive intimal

**FIGURE 1** The sinoatrial node (arrows) identified by the centrally placed SAN artery (A) merging imperceptively with the surrounding atrial myocardium (hematoxylin-eosin stain).

**FIGURE 2** The A-V conduction system in a SIDS infant. Top panel) Shown from left to right are A-V node and the proximal portion of His bundle. Bottom panel) Shown from left to right are the distal (branching) portion of the His bundle and the right and left bundle branches. All sections are hematoxylin-eosin stained; magnification is as indicated.
hyperplasia of the A-V node artery (table 2). By comparing the published illustrations of all other studies cited above and our own material, it seemed quite clear that there was an apparent moulding process of the A-V node and His bundle in the hearts of all infants under two years of age (figs. 2, 3 and 5). This moulding resulted from interdigitation of the CFB and conduction fibers rather than true replacement fibrosis. As Valdes-Dapena et al.6 have pointed out, the loosely woven pale-staining fibrous trigone (which stains positively for acid mucopolysaccharides) is characteristic of supporting connective tissue in infants, and not an area indicative of cell degeneration.

The other common finding in the conduction system of SIDS is hemorrhage, which also occurs just as frequently in

![Figure 3](image-url) - Schematic representation of figure 2. Note the resemblance of A-V conduction tissue to archipelagoes. AS = atrial septum; AVB = His bundle; AVN = atrioventricular node; CFB = central fibrous body; VS = ventricular septum; LB = left bundle branch; RB = right bundle branch.

![Figure 4](image-url) - Hemorrhage (HEM) in or around the conduction tissue. Left panel) The atrioventricular node (AVN). Right panel) The left bundle branch (LB). VS = ventricular septal myocardium. Hematoxylin-eosin stain.
ED infants (table 2). Despite the non-specificity of this finding and the possibility that it may reflect the outcome of terminal hypoxia rather than the cause, Ferris\textsuperscript{2} attached much significance to it and discussed evidence relating hemorrhage to arrhythmia and sudden death. In his study of 50 SIDS (no controls), Ferris\textsuperscript{2} found hemorrhage in 11 hearts in the region of the sinus node and internodal tracts. Although internodal tracts have been described,\textsuperscript{13} not all investigators are convinced of the histologic specialization of such tracts.\textsuperscript{14} We were unable to verify Ferris' findings, and in our own material hemorrhage occurred more commonly in or around approaches to the A-V node, the A-V node itself and the left bundle branch (fig. 4). Small petechiae were even more common outside the heart, notably in pleura, thymus and mediastinal lymph nodes.

Among the rarer findings in the conduction system of SIDS was an isolated bundle of specialized fibers in the membranous ventricular septum of two SIDS (fig. 6). These fibers apparently became separated from the A-V node as it emerged through the fibrous trigone as the His bundle. Since we did not identify any direct contact between these lost fibers and the working myocardium, we could not attach any functional significance to their existence in SIDS. Anderson et al.,\textsuperscript{7} on the other hand, described an accessory atrio-
ventricular connection in one SIDS infant, and they entertained the possibility that pre-excitation could exist through such pathways. Available evidence favors the concept that the cardiac conduction tissue develops in situ, the A-V node being formed from different primordia identifiable in the fetal heart by the cholinesterase staining reaction. Preliminary and ongoing studies by Anderson's group (R. H. Anderson, personal communication, June 5, 1975) thus far have been unable to identify any differences between SIDS and ED infants in the arrangement of cholinesterase-positive tissues.

Clearly the morphologic evidence of pathologic changes in the conduction system of SIDS is both circumstantial and equivocal. An earlier suggestion that an active destructive process takes place in the A-V node and His bundle, and therefore may be responsible for SIDS, cannot be substantiated by our own and other more recent studies. The discrepancy stems from differences in interpretation of histologic observations rather than different observations made by different groups of investigators. We are aware of the two common problems inherent in studies of this nature. First, there is no adequate all-purpose control group; valid controls for one factor may be invalid for another, and for others no valid controls are possible. Secondly, postmortem and agonal changes may confound accurate interpretation of some histologic findings. In analyzing our observations and in drawing our conclusions, we have taken these limitations into consideration. Without the corroboration of antemortem electrophysiologic studies, the functional significance of any abnormal or unusual morphologic findings in the conduction system of SIDS must in most cases remain conjectural. However, the prevailing concept of the mechanism of SIDS, possible autonomic instability affecting vital cardiorespiratory function, is most appealing. If examination of the conduction system in SIDS should become a routine, it is less likely that some subtle and as yet unrecognized abnormalities would escape our attention.

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