special report

Conduction System in Children with Acquired Immunodeficiency Syndrome*

Saroja Bharati, M.D., F.C.C.P.; Vijay V. Joshi, M.D.; Edward M. Connor, M.D.; James M. Oleske, M.D.; and Maurice Lee, M.D., F.C.C.P.

Six children died of acquired immunodeficiency syndrome (AIDS), four of them females, ages 7 months, 13 months, 2 years 8 months, and 4 years; and two of them males, aged 2½ and 7 years. They were born to IV drug-addicted parents. The conduction system (CS) and the entire heart were studied by serial section. In all cases the heart was hypertrophied and enlarged; one had total thrombotic occlusion of the right coronary artery with extensive infarction of the ventricular septum. Vascular changes also were found in all hearts, involving small arteries, arterioles, and venules. In the arteries, they involved the intima, media, and adventitia, and perivascular areas in a degenerative and inflammatory process. The elastic tissue was especially affected. A nonspecific myocarditis was present in four cases and epicarditis in all. Changes in the summit of the ventricular septum were present in four cases, consisting of increased fibrosis and arteriolosclerosis. The CS changes varied in location, showing either vasculitis, myocarditis, or fragmentation of the bundle with lobulation and fibrosis. The changes in the conduction system were not as severe as the changes in the surrounding myocardium. In one case the ECG was abnormal, showing left hemiblock. This corresponded to the finding of fibrosis, vacuolization of cells, and space formation in the left bundle branch.

(Chest 1985; 96:406-13)

CS = conduction system; HIV = human immunodeficiency virus

The histologic findings of the heart in acquired immunodeficiency syndrome (AIDS) in children* and in adults* have been described in the literature. Although various types of ECG abnormalities* have been documented clinically in children with AIDS, the conduction system thus far, to our knowledge, has not been studied pathologically. We therefore studied the conduction system and the entire heart in six children who died of AIDS.

MATERIALS AND METHODS

All six children were diagnosed to have AIDS and treated at Children's Hospital, Newark, NJ, where they died. There were four females and two males, and the ages ranged from seven months to seven years. All children were born to IV drug-addicted mothers and/or fathers, and some of the parents had AIDS and died of this disease. Antibody titers against human immunodeficiency virus (HIV) were measured by an enzyme-linked immunosorbent assay and confirmed by Western blot techniques. Each case showed defective cell-mediated immunity, indicated by skin anergy, reduced number of peripheral T cells, reversal of helper to suppressor T cell ratio, raised peripheral B cells, and polyclonal hypergammaglobulinemia. In all cases, culture of blood and urine done for bacteria, fungi, acid-fast organisms, and viruses were negative, except in case 1, where group B β-streptococcus and in case 3, where Candida were isolated. In cases 1 and 4 Candida was isolated from the esophagus and in case 1, Pneumocystis carinii from the lungs. In case 2, P carinii, herpes 1, and Candida were isolated from the lungs, and in case 4, Aspergillus was isolated from the lung. The complete autopsies were performed at Children's Hospital and have previously been reported. The hearts were fixed in 10 percent formalin solution and later submitted to two of us (S.B. and M.L.) for study of the conduction system. The gross findings in the heart are given in Table 1.

Conduction System Studies

Methods: The sinoatrial (SA) node and its approaches, the atrioventricular (AV) node and its approaches, and AV bundle, and

*From the Congenital Heart and Conduction System Center, The Heart Institute for Children of Christ Hospital and Medical Center, Oak Lawn, IL; Department of Pathology, Rush University-Presbyterian St. Luke's Medical Center, Chicago; Department of Pathology and Pediatrics, Children's Hospital of New Jersey, United Hospitals Medical Center, Newark; and University of Medicine and Dentistry of New Jersey—New Jersey Medical School, Newark; and Department of Clinical Pathology and Diagnostic Medicine, Greenville, NC.

Aided by grant HL 30558-06 from the National Institutes of Health, National Heart Lung and Blood Institute, Bethesda, MD.

Reprint requests: Dr. Bharati, Congenital Heart and Conduction System Center, 11743 Southwest Highway, Halsos Hts, IL 60463

406

Conduction System in Children with AIDS (Bharati et al)
### Table 1—Gross Autopsy Findings in the Heart

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Cardiomegaly</th>
<th>Chamber Size</th>
<th>Other Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>+</td>
<td>Biventricular hypertrophy and enlargement</td>
<td>Anomalous muscle bundle in left ventricle</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Anomalous distribution of coronary arteries</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hypertrophied supravalvular ridge</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Aneurysmal dilatation of ascending aorta</td>
</tr>
<tr>
<td>2</td>
<td>+</td>
<td>Biventricular hypertrophy and enlargement</td>
<td>Aneurysm of right coronary artery with thrombotic occlusion</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Infarction of ventricular septum</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dilatation of left ventricle</td>
<td>Aneurysmal dilatation of ascending aorta</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>High origin of both coronary ostia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dilatation of ascending aorta</td>
</tr>
<tr>
<td>3</td>
<td>+</td>
<td>Biventricular hypertrophy and enlargement</td>
<td>Hypertrophy of supravalvular ridge</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Left ventricular hypertrophy</td>
<td>Thickened mitral valve</td>
</tr>
<tr>
<td>4</td>
<td>+</td>
<td>Biventricular hypertrophy and enlargement</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>+</td>
<td>Biventricular hypertrophy and enlargement</td>
<td>—</td>
</tr>
<tr>
<td>6</td>
<td>+</td>
<td>Biventricular hypertrophy and enlargement</td>
<td>—</td>
</tr>
</tbody>
</table>

The bundle branches up to the level of the moderator band were serially sectioned. Every 10th or 20th section was retained in all of these structures up to the level of the muscle of Lancisi. Every 20th or 40th section was retained in the bundle branches more distally. The upper two-thirds of the atrial septum was serially sectioned, and every 40th section was retained. The remainder of the heart was cut into blocks, and two sections were taken from each block. Thus, the entire atrial septum and the ventricular septum to the level of the anterolateral papillary muscle of the right ventricle were serially sectioned as above, and most of the parietal wall of the right and left ventricle were cut into blocks and sampled. Alternate sections were stained with hematoxylin-eosin and Weigert-van Gieson stains. In this manner, a total of 1,392 sections were studied in case 1, 1,912 in cases 2, 1,632 in case 3, 2,252 in case 4, 2,460 in case 5, and 1,572 sections in case 6. This method of study has previously been described.** The findings were equated with those found in the normal hearts of the same age group.**

**Findings**

The findings in the conduction system and the entire heart are given in Tables 2 and 3.

The term myocarditis, as used in this article, implies an infiltration of mononuclear cells, with or without necrosis of the myocytes. This agrees with the terminology of Roldan et al.¹⁰ It does not agree with the terminology of Reilly et al.,²² Anderson et al.,²⁴ and Baroldi et al.,²⁵ who follow Aretz et al³¹ in calling a condition myocarditis only when, in addition to the infiltration of inflammatory cells, there is degeneration or necrosis of myocytes.

**Discussion**

The pathologic findings in the cases of AIDS in children¹¹ (with the exception of the heart) are (A) failure to thrive, (B) interstitial pneumonia of (a) Pneumocystis carinii type and (b) lymphoid interstitial type, (c) moderate to severe anemia, and (d) hepatosplenomegaly and ascites. Histologically there are marked arterial changes throughout the body. The small and medium-sized arteries show fragmentation of elastic fibers, calcification of the media, vasculitis, and perivasculitis. The heart in children²⁴,⁶,⁻⁸,¹¹ grossly shows cardiomyopathy with hypertrophy and dilatation of the right side and sometimes of the entire heart, and pericarditis with and without effusion. There may be thickening and nodularity of the tricuspid valve, and occasionally thrombosis of a main coronary artery. Histologically there is fragmentation of the elastic fibers of vessels with calcification, vasculitis, and perivasculitis. The immunologic findings, in addition to those mentioned for the adult, are atrophy of thymus, lymphoid depletion of the spleen, and Peyer's patches.

All of the hearts reported here were hypertrophied and dilated (Table 1). Aside from case 3, no cause for this hypertrophy was present in the main coronary arteries or in the valves. In case 3, there was thrombosis and occlusion of the beginning of the right
<table>
<thead>
<tr>
<th>Case No.</th>
<th>SA Node</th>
<th>Approaches to SA Node</th>
<th>Atrial Septum</th>
<th>Approaches to AV Node</th>
<th>AV Node</th>
<th>AV Bundle Penetrating</th>
<th>AV Bundle Branching</th>
<th>Left Bundle Branch</th>
<th>Right Bundle Branch</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No change</td>
<td>Increase in thickness of media of arterioles; fibrosis of epicardium w/ mononuclear cell infiltration</td>
<td>Mild to moderate fibrosis</td>
<td>Mononuclear cell infiltration w/ mild to moderate fibrosis; edema of fat tissue; dilatation of veins and lymphatics</td>
<td>Marked thickening of adventitia of small arteries and arterioles</td>
<td>Lobulation increase in connective tissue</td>
<td>No change</td>
<td>Increase in spaces; increased vacuolation of cells; Third part could not be followed</td>
<td>First part surrounded by fibrous tissue; Second part not identified</td>
</tr>
<tr>
<td>2</td>
<td>Mononuclear cells and neutrophils within and on periphery; epicarditis</td>
<td>Myocarditis Myocarditis w/ fibrosis (Fig 2)</td>
<td>Hemorrhage, mononuclear cells, and fibroblasts</td>
<td>Mono- nuclear cells; proliferation of intima and media of arterioles</td>
<td>No change</td>
<td>No change</td>
<td>Increase in spaces; fibrosis</td>
<td>First part—intramyocardial; fibrosis of first and second parts; third part could not be followed</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Slight fibrosis</td>
<td>Focal calcification in epicardium; arterioles thickened</td>
<td>Organizing infarct and myocarditis; calcification in internal elastic lamella of arteries (Fig 3) and arterioles</td>
<td>Fibrosis, myocardi- tis; disruption of elastic tissue; hemorrhage; infiltration of cells in adventitia of arterioles</td>
<td>Fibrosis and destruction of central fibrous body</td>
<td>Fibrosis; increase in spaces</td>
<td>Myocarditis; Thickening of adventitia of arteri- oles, w/infiltration of mononuclear cells</td>
<td>Calcification in first and second parts; third part not identified</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Recent thrombus in SA nodal artery, small hemorrhage</td>
<td>Epicarditis with hemorrhage; thickening of media of some arterioles; vein proliferation of intima and thickening of media</td>
<td>Fibrosis of nerves; fatty infiltration</td>
<td>Ramus septi fibrosis thickened and narrowed; proliferation of media, mononuclear cells in adventitia of arterioles</td>
<td>Moderate fibrosis; fatty infiltration of capillaries, w/ mononuclear cell infiltration</td>
<td>Fatty infiltration; fragmentation sandwiched between bulbar and main ventricular muscle (Fig 4)</td>
<td>Dilatation</td>
<td>Slight fibrosis</td>
<td>Fibrosis of first and second parts</td>
</tr>
<tr>
<td>5</td>
<td>No change</td>
<td>Epicarditis, myocarditis, hemorrhagic cardiomyopathy</td>
<td>Fibrosis and thickening of adventitia w/infiltration</td>
<td>Thickening of adventitia w/infiltration</td>
<td>No change</td>
<td>No change</td>
<td>Increase in spaces w/ fibrosis w/vacuolar</td>
<td>First part surrounded by fibrotic tissue; second part (continued)</td>
<td>Conduction System in Children with AIDS (Bharati et al)</td>
</tr>
<tr>
<td></td>
<td>Rhage, fibrosis, neuritis fibrosis of adventitia w/ mononuclear cell proliferation of small arteries and arterioles</td>
<td>Ventitia of arterioles w/ infiltration of mononuclear cell proliferation of small arteries (Fig 5)</td>
<td>Ventitia of cells of AV nodal artery</td>
<td>Lar degeneration of Purkinje cells</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
<td>Enlargement of spaces</td>
<td>First part intramyocardial, myocarditis in end of second and beginning of third parts</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>6</td>
<td>No change</td>
<td>Epicarditis; calcification of media w/ mononuclear cells in adventitia</td>
<td>Proximalization of muscle of media w/fibrosis of adventitia, mononuclear cells in adventitia, calcification of media of small arteries</td>
<td>No change</td>
<td>Fatty metamorphosis, hemorrhage and fat necrosis; vascular changes; fibrosis of nerves and calcification of myocytes and nerves</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
<td>Enlargement of spaces</td>
</tr>
</tbody>
</table>

**Figure 1.** Case 1. Marked thickening of the adventitia of small arteries and arterioles, by collagenous tissue in the AV node (Weigert-van Gieson, original magnification x 45). N = AV node; A = atrial septum; V = ventricular septum.

**Figure 2.** Case 2. Myocarditis in the atrial septum (Hematoxylin-eosin, original magnification x 150).
Figure 3, Case 3. Small artery in atrial fat tissue showing degenerative changes with calcification in the internal elastic lamella with an infiltration of mononuclear cells in the adventitial and in the fat tissue adjacent (Hematoxylin-eosin, original magnification ×150). F = fat tissue.

Figure 4, Case 4. Area of fragmentation of the lower part of the bundle with Mahaim fibers going into the ventricular septum with increased fibrosis of the ventricular septum (Weigert-van Gieson, original magnification ×22). B = bundle of His; AM = aortico-mitral anulus; V = ventricular septal musculature; A = atrial septal musculature; Arrows demarcate the area of fragmentation of the bundle, mahaim fibers, and summit of the ventricular septum.

Figure 5, Case 5. Increase in adventitia of small artery in atrial septum, with thickening of collagen fibers and an infiltration of mononuclear cells in adventitia and periaxial tissue (Hematoxylin-eosin, original magnification ×60). A = atrial septal myocardium. Arrows delineate the artery.

coronary artery with infarction of the ventricular septum. The hypertrophy of the supravalvular ridge in cases 1 and 5 was apparently not obstructive. Histologically, however, there was considerable nar-

Figure 6, Case 3. Calcification of a branching arteriole in the summit of the ventricular septum, with an increase in collagenous tissue in the adventitia of the branch. Calcium is present in the lumen and wall (Hematoxylin-eosin, original magnification ×225). M = myocytes. Arrows point to the branching arteriole.
## Table 3—Histologic Findings in Other Areas of the Heart

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Summit of Ventricular Septum</th>
<th>Central Fibrous Body</th>
<th>Aortic Valve</th>
<th>Left Atrium and Ventricle</th>
<th>Right Atrium and Ventricle</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Focal fibrosis slight infiltration of mononuclear cells; marked thickening and narrowing of some large arterioles and small arteries, fibrosis on left side</td>
<td>Basophilic degeneration</td>
<td>No change</td>
<td>Thickening and narrowing of large arterioles, increased fibroelastosis of endocardium</td>
<td>Periarterial fibrosis of myocardium and epicardial fibrosis</td>
</tr>
<tr>
<td>2</td>
<td>Increase in collagen, fibroblasts, and mononuclear cells in adventitia of arterioles</td>
<td>No change</td>
<td>Vacular, basophilic degeneration of spongiosa</td>
<td>Chronic epicarditis; Perivascular fibrosis throughout myocardium</td>
<td>Epicarditis, myocarditis</td>
</tr>
<tr>
<td>3</td>
<td>Organized infarct; arteries proliferation of intima, destruction of internal elastic lamella, degeneration in media and mononuclear cells in adventitia; increase in connective tissue on left side; myocarditis fibrosis of nerve; calcified material in lumen of arterioles (Fig 6)</td>
<td>Enlarged; areas of hemorrhage</td>
<td>Basophilic degeneration of spongiosa</td>
<td>Myocarditis; thickening of adventitia of vessels</td>
<td>Myocarditis; calcification of myocytes, epicarditis; degeneration of elastics of vessels w/ calcification</td>
</tr>
<tr>
<td>4</td>
<td>Increase in connective tissue left side; proliferation of intima and media of large arterioles; dilatation of lymphatics</td>
<td>No change</td>
<td>Vacuolization of spongiosa</td>
<td>Epicarditis; thickening of small arterioles, mononuclear cell infiltration of myocardium</td>
<td>Fibrosis</td>
</tr>
<tr>
<td>5</td>
<td>Marked increase in connective tissue; thickening of intima with proliferation of adventitia (Fig 7)</td>
<td>No change</td>
<td>Vacular degeneration of spongiosa</td>
<td>Epicarditis; vascular changes of arteries and arterioles as elsewhere in myocardium</td>
<td>Epicarditis; vascular changes as elsewhere in myocardium</td>
</tr>
<tr>
<td>6</td>
<td>Increase in fibroelastosis of both sides; marked arteriolosclerosis; fibrosis of nerves</td>
<td>No change</td>
<td>Increased, vacuolated spongiosa</td>
<td>Epicarditis and periartheritis in myocardium</td>
<td>Epicarditis; mononuclear cells around vessels in myocardium</td>
</tr>
</tbody>
</table>

Narowing of some of the small coronary arteries and arterioles in all cases, which could be a cause of the hypertrophy. Likewise, the presence of myocarditis in four cases could produce hypertrophy. It is doubtful whether the epicarditis present in all cases would be a cause of hypertrophy.

The histologic changes in the heart in our cases which deserve discussion in addition to the changes in the conduction system are: (1) the vascular changes, (2) the myocarditis and epicarditis, and (3) the sclerosis in the summit of the ventricular septum.

The vascular changes are most outstanding, and the findings extend those mentioned in the literature. The least change was the hypertrophy of the smooth muscle of the media, proliferation of the collagenous tissue of the adventitia, and perivascular increase in connective tissue. These were present in all six hearts in the small arteries and arterioles. The adventitia and the perivascular areas in these vessels were infiltrated with mononuclear cells and fibroblasts. In some cases, the cells of the intima were also proliferated.

A more advanced change in the coronary arteries was seen in case 3. This involved the main coronary arteries as well as the smaller arteries. Here, the internal elastic lamella was disrupted and calcified. The calcific masses so produced pressed on the surrounding layers of the arteries. In other cases, masses of calcific material replaced all or part of a vessel wall and in some cases filled the lumen. The external elastic lamella was similarly involved in some
FIGURE 7, Case 5. Large arteriole in the ventricular septum showing proliferation of the intima and the collagenous tissue of the adventitia (Weigert-van Gieson, original magnification × 300). V = ventricular septal musculature. Arrow points to the arteriole.

Arteries. Degenerative changes were seen in the smooth muscle of the media, with changes as previously described in the adventitia. Veins and capillaries showed proliferative and in some cases calcific changes. The changes in the elastic tissue are similar and extend those reported previously.2

An epicarditis was found over the entire heart in all. A nonspecific myocarditis was found in cases 2, 3, 5, and 6. In cases 2 and 6, this involved the atrial septum and the right ventricle. In case 3, it was found in the atrial and ventricular septa. In case 5, it involved the atrial septum. What is the cause of this myocarditis? It may be an extension of the epicarditis, or both the myocarditis and epicarditis may be due to the inflammatory changes in the vascular tree. They are not directly related to known organisms, as these were not found histologically by us, or cultured from the myocardium at the Children’s Hospital. Whether they are related to products of organisms not yet isolated or to an autoimmune mechanism is not within the realm of the present discussion.

The pathologic changes in the summit of the ventricular septum in our cases are of interest. We have previously studied these changes in the young and with advancing age.38-39 They consist of increased fibrosis of the summit with various secondary degenerative changes and arteriolsclerosis. They come on normally after the age of about 40. In our cases 1, 3, 4, and 5, these changes were very severe. This is completely abnormal in small children. These changes may be important in the genesis of conduction system lesions.

The pathologic changes in the conduction system varied from case to case. In general, vascular changes including thrombosis were noted in the SA and/or the AV nodes similar to those described in the surrounding myocardium. However, a myocarditis was noted in one SA node and in the second and third part of the right bundle branch in another case. Parenchymal changes were noted in the AV bundle and the left bundle branch. All of these changes are not as severe as those seen in the myocardium of the atria and ventricles in our cases.

Electrocardiograms were taken in cases 1, 4, 5, and 6, and were negative in cases 1, 4, and 6. In case 5, however, there was left anterior hemiblock. This corresponds well with the fibrosis, vacuolization of cells, and space formation seen in the left bundle branch in this case.

In the literature, ECG abnormalities in cases of AIDS in children and adults have been noted. This includes right axis deviation, right ventricular hypertrophy, left ventricular hypertrophy, T-wave changes, right bundle branch block, ST-T-wave abnormalities, and ventricular tachycardia.43-45 It can therefore be anticipated that changes in conduction and the conduction system of a mild or severe nature will be reported in future cases of AIDS.

The changes in the conduction system in our cases may be related to various causes. The marked increase in fibrosis of the summit of the ventricular septum, which was present in most cases, can produce degenerative and fibrotic changes in the bundle and bundle branches. The SA node lies adjacent to the epicardium. Changes in the SA node may thus be related to the epicarditis that was present in all cases. The vascular changes in the conduction system and the myocarditis of the right bundle branch in case 6 are part of the general vasculitis of the heart in AIDS.

The conduction system, the entire myocardium, and the fibrous skeleton of the heart are affected in children who have AIDS. The changes in the conduction system are less severe than those in the myocardium. In some cases the atria are more involved than the ventricles, and sometimes the right ventricle more than the left ventricle. The common denominator that
emerges in the pathologic change is the vascular changes. These changes may involve the larger coronary arteries to be accompanied by thrombosis and infarction. In the large, medium, and small coronary arteries, a prominent feature in the pathology is the involvement of the elastic tissue. In the small coronary arteries and arterioles, the periarteritis stands out. The venules and capillaries are also involved. The relationship of this pathologic change to infantile periarteritis nodosa, Kawasaki’s disease, and collagen disease needs further elucidation. It is not known whether the changes are primarily due to the HIV virus or to its antibody or are secondary to the immune deficiency phenomenon. To date, we are not aware of any experimental data showing that the HIV virus affects blood vessels directly.

REFERENCES