PATHOPHYSIOLOGY AND NATURAL HISTORY
CONGENITAL HEART DISEASE

Pathologic features of myocardial hamartomas causing childhood tachyarrhythmias

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ABSTRACT We have observed in 11 infants, aged 2 years or less, a distinct clinicopathologic lesion responsible for tachyarrhythmias that were fatal in 96% (25/26) of previously reported cases. Nine of the 11 patients, who underwent electrophysiologic mapping and surgical excision of the lesion, have survived, with follow-up periods ranging from 1 month to 6 years. The morphologic findings in these 11 patients and in the 26 cases cited in the literature are reviewed. Pathogenic considerations have included viral-induced lesions, cardiomyopathy, neoplasm, and developmental disorder of Purkinje cells. We believe this lesion to be a myocardial hamartoma. Supportive evidence includes prevalence in infants, tumorlike growth pattern without mitotic figures, and association of other developmental abnormalities. Through electrophysiologic mapping, this myocardial hamartoma is potentially accessible to surgical excision and long-term cure. Circulation 75, No. 4, 705-710, 1987.

POTENTIALLY FATAL ventricular tachycardia in children 2 years old or younger may be caused by a localized myocardial abnormality that has been termed arachnocytesis of the heart muscle, isolated cardiac lipidosis, infantile cardiomyopathy with histiocytoid reaction, infantile xanthomatosus cardiomyopathy, focal lipid cardiomyopathy, focal myocardial degeneration, foamy myocardial transformation of infancy, idiopathic infantile cardiomyopathy, histiocytoid cardiomyopathy of infancy, oncocytic cardiomyopathy, and Purkinje cell tumor. Currently, electrophysiologic mapping may localize the abnormality so that curative surgical excision can be performed for this previously fatal condition. In this study we present the morphologic findings in 11 recently treated patients (nine of whom survived), review previously reported cases, and discuss concepts of pathogenesis of this peculiar myocardial lesion. These 11 patients, who were referred to our institution between 1980 and 1986 because of symptomatic ventricular tachycardia, were found at operation to have a distinct morphologic lesion.

Methods
Clinical evaluation included chest roentgenogram and two-dimensional echocardiography. All patients underwent intracardiac electrophysiologic study with localization of the earliest site of endocardial activation. Surgical excision of the arrhythmogenic area was performed with cryoablation of the margins. Surgically excised myocardium was placed in Zenker’s fixative for routine histologic examination, and sections were stained with hematoxylin and eosin, a modified Gomori’s trichrome stain for connective tissue, and the periodic acid–Schiff stain for glycogen. Electron microscopic studies were performed on myocardium from eight of the 11 patients, with 2.5% glutaraldehyde fixation and staining with uranium acetate/lead citrate. An autopsy was performed on one of the two infants who died, and the heart, including the conduction system, was examined extensively.

Results
The clinical features pertinent to this report are summarized in table 1. The age of onset of ventricular arrhythmia ranged from 3 weeks to 28 months. All 11 patients had symptomatic ventricular tachycardia with rates ranging up to 428 beats/minute and three had ventricular fibrillation. Most patients had mild cardiomegaly on chest roentgenogram. Two-dimensional echocardiography demonstrated normal cardiac anatomy in all patients; most had decreased left ventricular function. Since none of the patients responded well to conventional antiarrhythmic drug therapy, the arrhythmogenic areas were localized with electrophysiologic mapping and surgically excised. In nine patients, discrete left ventricular lesions were identified. The re-
KEARNEY et al.

TABLE 1
Clinical summary

<table>
<thead>
<tr>
<th>Patient</th>
<th>Onset VT</th>
<th>At Op.</th>
<th>Race/sex</th>
<th>Clinical findings</th>
<th>EPS localization</th>
<th>Postoperative course</th>
<th>Associated morphologic findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1‡</td>
<td>0.8</td>
<td>19.0</td>
<td>W/F</td>
<td>VT, CA with seizures, fever, vomiting</td>
<td>LV apex</td>
<td>Asymptomatic, NSR at 6 yr follow-up</td>
<td>—</td>
</tr>
<tr>
<td>2‡</td>
<td>8.8</td>
<td>9.5</td>
<td>LA/F</td>
<td>VT URI 3 wk PTA at age 8 mo</td>
<td>Posteroapical LV</td>
<td>Asymptomatic, NSR at 3 yr 5 mo follow-up</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>19.0</td>
<td>20.0</td>
<td>W/M</td>
<td>VT, VF, CA with seizures</td>
<td>Apicoseptal LV</td>
<td>JR and pacemaker insertion; asymptomatic at 1 yr 10 mo follow-up</td>
<td>Laryngeal web ASD</td>
</tr>
<tr>
<td>4</td>
<td>21.0</td>
<td>21.0</td>
<td>W/F</td>
<td>VT, viral illness at age 20 mo</td>
<td>Anteroapical LV</td>
<td>Asymptomatic, NSR at 1 yr follow-up</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>13.5</td>
<td>16.75</td>
<td>B/M</td>
<td>VT, fever, rash, seizure</td>
<td>Posterior LV</td>
<td>Asymptomatic at 7 mo follow-up</td>
<td>—</td>
</tr>
<tr>
<td>6</td>
<td>14.75</td>
<td>15.75</td>
<td>LA/M</td>
<td>VT and CHF URI 3 wk PTA at age 14 mo</td>
<td>Posteroapical LV</td>
<td>Asymptomatic, NSR at 2 mo follow-up</td>
<td>PFO</td>
</tr>
<tr>
<td>7</td>
<td>28</td>
<td>32</td>
<td>W/F</td>
<td>SVT at age 1 day URI with VT at 28 mo</td>
<td>Apicoseptal LV</td>
<td>NSR at 2 mo follow-up</td>
<td>PFO</td>
</tr>
<tr>
<td>8</td>
<td>7.5</td>
<td>8.5</td>
<td>W/M</td>
<td>URI with VT</td>
<td>Posteroapical LV</td>
<td>Asymptomatic, NSR at 2 mo follow-up</td>
<td>—</td>
</tr>
<tr>
<td>9</td>
<td>1.5</td>
<td>3.5</td>
<td>W/F</td>
<td>SVT 6 mo in utero VT, VF, CA at 1.5 mo</td>
<td>Apical LV RVOT</td>
<td>2nd surgical resection at 1 wk, CHF and death at 3 mo follow-up</td>
<td>—</td>
</tr>
<tr>
<td>10</td>
<td>12</td>
<td>14</td>
<td>W/F</td>
<td>VT, CA</td>
<td>Anteroapical LV</td>
<td>Asymptomatic, NSR at 1 mo follow-up</td>
<td>—</td>
</tr>
<tr>
<td>11‡</td>
<td>3.5</td>
<td>4.5</td>
<td>W/F</td>
<td>VT, VF, CA with seizures</td>
<td>LV, RVOT</td>
<td>Low-output cardiac failure and death at 18 hr</td>
<td>(L) microphthalmos, bilateral oblong pupils, hazy corneas</td>
</tr>
</tbody>
</table>

VT = ventricular tachycardia; Op. = operation; EPS = electrophysiologic studies; CA = cardiac arrest; LV = left ventricle; NSR = normal sinus rhythm; URI = upper respiratory infection; PTA = prior to admission; VF = ventricular fibrillation; JR = junctional rhythm; ASD = atrial septal defect; CHF = congestive heart failure; PFO = patent foramen ovale; SVT = supraventricular tachycardia; RVOT = right ventricular outflow tract; L = left; W = white; B = black; LA = Latin American.

‡The ASD, PFOs, and laryngeal web were surgically repaired.

‡The clinical features of these cases have been previously reported.15

remaining two patients (Nos. 9 and 11) had extensive biventricular tumor that could not be excised completely; one died in the immediate postoperative period and the other died 3 months after operation. All survivors are without arrhythmia and have improved ventricular function.

In 10 of the 11 patients, the surgically excised myocardium contained tan-white foci on either the epicardial or endocardial surface and poorly defined pale tan discoloration of the myocardium. The amount of excised tissue per patient varied from approximately 1 × 1 × 1 cm to 5 × 3 × 1 cm; microscopically the abnormal foci occupied from less than 1% (patient 5) to 80% (patient 9) of the surface area of the tissue.

Histologically, the abnormal foci were relatively sharply demarcated aggregates of round to polygonal cells that were up to twice the size of adjacent myocardial cells. The aggregates were subendocardial in patients 1, 3, 4, 6, 7, 9, 10, and 11 and subepicardial in patients 1, 2, 4, 5, 8, and 11. Exclusively subepicardial location (figure 1) generally correlated with the smaller lesions. Individual cells had distinct cytoplasmic borders and variable numbers of fine or coarse eosinophilic granules in the cytoplasm; the degree of granulation was responsible for the variation in appearance from pale to eosinophilic cells (figure 2). No cross-striations were visible. The nuclei usually were large and hyperchromatic with irregular convoluted borders and a prominent nucleolus. Occasional cells were multinucleate. No mitotic figures could be identified. Fibrous stroma in and about groups of cells varied from prominent (patients 2 and 5) to slight (patients 1, 4, and 7). Scattered lymphocytes, occasionally in small clusters, were present in nine of the 11 patients.
The myocardial fibers adjacent to the abnormal collections of cells were mildly hypertrophic in most cases. In five patients (Nos. 3, 5, 6, 7, and 11) the adjacent myocardium had focal areas of loss of myocytes, replacement fibrosis, and mild-to-moderate interstitial fibrosis. Endocardial sclerosis, present in all 11 patients, ranged from slight to moderate. The degree of sclerosis did not correlate with either the size of the lesion or an endocardial location; patient 5, for example, had the smallest lesion, which was exclusively subepicardial, and had focal moderate endocardial fibrosis.

Electron microscopic studies demonstrated abnormal cells that were generally round to oval with smooth cytoplasmic borders (figure 3). The basement membrane was thin and inconspicuous in patients 2 and 11 but exhibited reduplication that was mild in patients 1, 8, and 9 and focally marked in patients 3 and 4. Scattered desmosomes were present, but intercalated discs and T tubules were not clearly identified. The most striking fine structural feature was a marked increase in the number, and focally the size, of mitochondria (figure 4). The mitochondrial cristae varied from disorganized, vesicular, or closely opposed dense layers to apparent circular profiles. Occasional round or linear, dense mitochondrial inclusions were seen. Glycogen granules were present in some mitochondria in patients 2, 3, 6, 8, 9, and 11. In some cells, a few structures of a residual body type were present; some were dense and some had a lamellar structure. The few myofibrils that could be identified in these cells were small, disorganized, peripherally located segments of sarcomeres with focal accentuation of the Z bands. Leptofibrils (figure 5) were found in patients 3, 4, 6, 8, 9, and 11 and leptofibrill-like structures were present in patient 2. Cytoplasmic lipid was mildly to moderately increased and glycogen was either normal or mildly increased.

In one of the fatal cases (patient 11), autopsy showed mild cardiomegaly, 41 g (30 g normal weight). The aggregates of abnormal cells just described were present diffusely in the left ventricular endocardium,
left ventricular papillary muscles and chordae tendineae, right ventricular outflow tract, limbus fossa ovalis of the right atrium, on the atrial surface of the tricuspid valve (figure 6) as two discrete 2 mm nodules, and scattered diffusely throughout much of the ventricular myocardium. Additionally, similar cells were present in the vicinity of both sinoatrial and atrioventricular nodes.

Discussion

The lesion described represents a distinct clinico-pathologic entity that has been reported in 37 patients, including the 11 described herein. The age, clinical presentation, light microscopic and ultrastructural features are characteristic. The ages of affected children ranged from birth to 28 months (mean 11.88 months), and the majority of patients were females (30 of 37). The major clinical manifestations were uncontrollable tachyarrhythmias. Sixteen children, including four with sudden death, died within 1 week of the onset of an arrhythmia.

Cardiomegaly was described in 17 of 20 patients in whom heart weights were recorded. The heart has been described as either flabby and dilated or hypertrophied. Associated cardiac abnormalities reported included ventricular septal defect, atrial septal defects (ref. 15a and patient 3), and “classic” endocardial fibroelastosis. Lesions represented by areas of pallor or grey-yellow discoloration were visible in most cases. Valve nodules were grossly visible in 10 patients and found microscopically in two others. Although lesions have been described on all four cardiac valves, the mitral valve was most often involved (11 patients) and the pulmonary valve rarely (one patient). The left ventricle was the most frequent chamber involved, particularly the subendocardial myocardium. Isolated atrial lesions have occurred. Epicardial nodules have been described and specified as being peripheral to the normal limits of muscle and peripheral to the coronary
vessels. Lesions in or near the cardiac conduction system have been previously reported in 14 of 15 patients for whom the information is available.

Electron microscopy was performed in 21 patients, including eight of the 11 described here. The abnormalities of the myofibrils and mitochondria were consistent findings. Leptofibrils were described in nine patients. Cytoplasmic lipid and glycogen content were highly variable, and intramitochondrial glycogen was present in nine patients.

The rapidly fatal clinical course among the patients from the literature contrasts with the longer duration of arrhythmia in the 11 new patients, most of whom had had ventricular arrhythmia for at least 1 month. Despite the five patients (table 1, Nos. 1, 3, 9, 10, and 11) who experienced cardiac arrest, there were no instances of sudden death. In a review of all 37 patients, no correlations between the clinical course and the location or extent of the lesion were identifiable. Although involvement of the conduction system may be a significant prognostic factor, this information is not available for many of the patients, including three of the four reported cases of sudden death. The one previously reported survivor of this condition had arrhythmias for 3 months and had apparent involvement of the bundle of His. The conduction system was presumed to be unaffected in the nine survivors reported here. Since most of the 11 new patients were referred to our institution after the arrhythmia had persisted for 3 to 4 weeks, the absence of rapidly fatal cases may reflect a selection bias. Gross myocardial lesions are not uniformly present and may cause some cases to go unrecognized and other cases may be unreported.

Different interpretations as to the exact nature of these tumorlike aggregates and their pathogenesis are reflected in the variety of terms applied. Early studies considered the cells to be lipid-filled histiocytes, but since the electron microscopic description by Haese et al., their myocytic nature has been well established.

Pathogenic considerations have included viral-induced lesions, cardiomyopathy, neoplasma, and developmental disorder of Purkinje cells. One reported case had circumstantial evidence suggesting that a viral effect in early development could have produced the lesions; the few reports of viral cultures, however, have been negative and viral particles have not been demonstrated by electron microscopy.

Cardiomyopathy has been suggested because of the paucity of myofibrils in the abnormal cells and the presence of cardiomegaly. Myocardial cells with a partial loss of myofibrils, and/or increased mitochondria separating the fibrils, have been interpreted as being intermediate, less severely affected myofibers and have been termed "transitional cells." These "transitional cells" have been offered as further supportive evidence of a cardiomyopathic disease process. We observed scattered myocytes with a variable, though generally mild, loss of myofibrils and an increase in mitochondria. Such myocytes retained the normal elongated, parallel orientation and were not significantly larger than the adjacent normal myocardial cells. We interpret these cellular abnormalities as being indicative of mild degenerative changes. Cardiomegaly, hypertrophy, focal fibrosis, and myocardial degenerative changes correlate with the clinical findings of myocardial dysfunction and may, in part, represent the effects of prolonged arrhythmia. The localized collections of the abnormal cells, and the apparent successful cure of the condition by surgical excision, argue against cardiomyopathies as they are currently understood. One reported instance of cardiomyopathy associated with deficiency of myocardial cytochrome B does not appear to be this clinicopathologic entity since the baby's illness began with failure to thrive and led to a fatal cardiac arrest without reported arrhythmia.

Amini et al. believed that the strikingly different morphologic appearance of these rounded myocytes, as compared with the surrounding myocardium, reflected an intrinsically distinct population of cells that were considered to belong to the Purkinje network. Zimmerman et al. and Rossi et al. also favored a developmental disorder or tumor of Purkinje cells. The predominant subendocardial location, frequent involvement of the conduction system, positive histochemical staining for cholinesterase, primitive ultrastructural morphology, and clinical presentation with uncontrollable arrhythmias were cited as supportive features. The occasional epicardial or valvular location of lesions and surgical cure by excision of discrete lesions, however, are not consistent with the view that the conduction system proper is abnormal.

We believe that these lesions represent an abnormality of cardiac development of a hamartomatous nature. The features of a hamartoma that are illustrated by this lesion include location of the cellular aggregates in parts of the heart in which the cell type may be found normally or heterotypically, a tumorlike growth pattern that is relatively proportionate to the surrounding normal tissue with no apparent mitotic figures, the prevalence in infants suggesting that the lesion may have been present at birth, and the association of developmental abnormalities in other organs (table 2).
The constituent large, rounded cells with few myofibrils suggest a primitive myocyte morphology. Similar considerations have led to the classification of cardiac rhabdomyomas as hamartomatous malformations.21,22 Cardiac rhabdomyomas are also composed of large rounded cells with few myofibrils but invariably have increased cytoplasmic glycogen and lack the proliferative mitochondrial abnormalities seen in the lesions reported here. In view of these considerations, we currently believe this condition is best regarded as a hamartomatous malformation that is distinct from the cardiac rhabdomyoma. Whether the cell of origin of this lesion is a Purkinje cell or a nonspecific myocardial cell cannot be definitely established at this time.

Through electrophysiologic mapping, this myocardial hamartoma is potentially accessible to surgical excision and long-term cure. Involvement of the conduction system may occur and require a pacemaker. Without surgical intervention the course appears to be rapidly and invariably fatal, so that early recognition of the characteristic clinical presentation of this benign myocardial hamartoma is essential.

We appreciate the technical assistance with electron microscopy by Dr. Hal K. Hawkins and Mr. James P. Barrish and the secretarial assistance of Mrs. Lillian O’Neil.

References

### Table 2

<table>
<thead>
<tr>
<th>Anomaly</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corneal opacities (4)</td>
<td>1, 9, 11, patient 11</td>
</tr>
<tr>
<td>Microphthalmos (3)</td>
<td>9, 11, patient 11</td>
</tr>
<tr>
<td>Hydrocephalus (2)</td>
<td>9, 12</td>
</tr>
<tr>
<td>Agenesis of corpus callosum (2)</td>
<td>9, 11</td>
</tr>
<tr>
<td>Microcephaly (1)</td>
<td>18</td>
</tr>
<tr>
<td>Poly microgyria (1)</td>
<td>9</td>
</tr>
<tr>
<td>Deficient occipital cortex (1)</td>
<td>9</td>
</tr>
<tr>
<td>Megalocornea (1)</td>
<td>11</td>
</tr>
<tr>
<td>Oblong pupils (1)</td>
<td>Patient 11</td>
</tr>
<tr>
<td>Cataract (11)</td>
<td>11</td>
</tr>
<tr>
<td>Aphakia (1)</td>
<td>11</td>
</tr>
<tr>
<td>Laryngeal web (1)</td>
<td>Patient 3</td>
</tr>
<tr>
<td>Meckel’s diverticulum (1)</td>
<td>Patient 11</td>
</tr>
</tbody>
</table>

*Numbers in parentheses reflect the number of patients with the anomaly.*
Pathologic features of myocardial hamartomas causing childhood tachyarrhythmias.
D L Kearney, J L Titus, E P Hawkins, D A Ott and A Garson, Jr

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