Familial Congenital Complete Heart Block and Maternal Systemic Lupus Erythematosis

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SUMMARY  A family is reported in which two siblings had congenital complete heart block with resultant congestive heart failure, the father and paternal grandfather show adult-onset conduction defects, and the mother has systemic lupus erythematosis. The interaction of heredity and environment is discussed in this context. A review of the literature on familial complete heart block suggests that so-called pure congenital-onset familial heart block, originally felt to be genetic, may in fact have an important environmental component, specifically related to ongoing maternal factors such as systemic lupus erythematosis.

FAMILIAL COMPLETE HEART BLOCK (CHB) has been described by a number of observers since the report by Morquio in 1901. Among those reported are thirteen families with multiple cases of well-documented congenital CHB using the classic criteria of Yater and eliminating those with intracardiac defects. More recently, an association has been noted between CHB and maternal connective tissue disease (CTD), particularly systemic lupus erythematosis (SLE). Among cases not reported in relation to maternal SLE, we would like to report a kindred revealing a genetic-environmental interaction between the above factors, which has not been noted in the medical literature. Previously reported cases of familial block will be analyzed in the light of this new information.

Case Reports

The proband of our kindred (case 1, W.S.) prompted an investigation which has revealed previously unrecognized factors in the death of a sibling and in surviving family members. Paternal transmission of CHB through three generations and maternal SLE were uncovered. The five most informative family members will be discussed (see fig. 1).

Case 1. W.S., the proband (IV-2 in fig. 1), is a white female infant. Fetal bradycardia at a rate of 70/min was noted at 24 weeks gestation. At no time was the fetal heart rate normal. The infant was delivered by elective repeat Cesarean section at term with Apgar scores of 6 at both 1 and 5 minutes. Physical examination revealed a vigorous acyanotic infant with a left parasternal lift and a grade II/V harsh systolic murmur at the upper left sternal border. S1 and S2 were normal for age. The liver edge was palpable 6 cm below the right costal margin and the spleen edge 3 cm below the left costal margin. Electrocardiogram (ECG) showed complete heart block with atrial rate 150/min, ventricular rate 68/min, and right atrial enlargement and right ventricular hypertrophy. Chest X-ray showed marked cardiomegaly and prominent pulmonary vascularity. Echocardiogram showed normal anatomy and mild left atrial enlargement. A diagnosis of congenital CHB with congestive heart failure was made, and the patient was treated with digoxin and furosemide. A gradual improvement in the cardiomegaly and visceromegaly was noted. The hospital course was complicated by thrombocytopenia with a platelet count of 40,000 at birth rising to 195,000 at 8 days of age. No bleeding diathesis was noted and no specific therapy given.

At 13 days of age a rash appeared on the head and within one week became generalized (fig. 2). The lesions were annular erythematous patches with central clearing. Skin biopsy showed liquefaction degeneration of the basal zone, consistent with discoid lupus erythematosis, but with negative immunofluorescence. Serum complement was normal at 54, and antinuclear antibody (ANA) speckled positive at a titer less than 1:64. A diagnosis of congenital lupus erythematosis was made. She was treated with topical steroids with gradual resolution of the rash.

Case 2. B.S. (III-7 in fig. 1), mother of W.S. and T.S., is a 28-year-old white female, now gravida 2 para 2 living children 1. She has a history of hypothyroidism without thyroiditis since age 15 and currently takes synthroid 0.5 mg daily. Since age 5 she has had intermittent arthralgias and morning stiffness, and at 18 had an exacerbation of these symptoms accompanied by low grade fever. During her second pregnancy (see case 1), ANA was negative. When the diagnosis of congenital lupus was made on W.S., further evaluation showed the following: ANA strongly positive at 1:256; sedimentation rate 46; rheumatoid factor positive at 1:1160; skin biopsy with immunofluorescence speckled positive; and VDRL negative. A diagnosis of SLE with minimal clinical expression was made. As the patient was adopted in infancy, her family history is unknown and no relatives are available for study.

Case 3. Two years prior to the birth of our proband, a female sibling, T.S. (IV-1 in fig. 1), was delivered by emergency Cesarean section for fetal bradycardia at 60–80/min. Previous fetal heart rate was not reported as abnormal. Apgar scores were 1 at one minute and 5 at five minutes, and the infant was grossly meconium stained. Examination revealed cyanosis, marked respiratory distress,
diffuse petechiae and ecchymoses, a grade I-II/VI systolic murmur at the left sternal border, and massive hepatosplenomegaly. Laboratory studies revealed anemia, hypoxemia, mixed respiratory and metabolic acidosis, and disseminated intravascular coagulation. The chest X-ray showed marked cardiomegaly with bilateral pulmonary infiltrates and the ECG revealed complete heart block with an atrial rate of 120/min and a ventricular rate of 58/min. Despite vigorous medical intervention including mechanical ventilation, exchange transfusion, parenteral antibiotics and pressor agents, the infant died at 21 hours of age.

Postmortem examination revealed large amounts of meconium in the alveoli and terminal airways. The spleen and liver were severely enlarged with extensive extra-medullary hematopoiesis and iron deposition. Granulation tissue without acute infiltration of leukocytes was found sub-pericardially and there were scattered subendocardial calcium deposits. The conduction system was not studied. Viral and bacterial cultures were negative and viral titers unremarkable.

Case 4. J.S. (III-6 in fig. 1), father of W.S. and T.S., is a 26-year-old white male whose past medical history is unremarkable, with the exception of episodes of asymptomatic bradycardia at 40/min during his adult years. No abnormal cardiac rhythms, heart murmurs, or syncopal episodes were noted in childhood. The ECG currently shows a wandering atrial pacemaker with a rate varying from 47 to 75/min, PR interval 0.16 sec and QRS duration of 0.06 sec. Physical examination is unremarkable.

Case 5. A.S. (II-1 in fig. 1), father of J.S., is a 50-year-old white male who presented at age 41 with palpitations and exertional dyspnea. He had no previous history of cardiac or coronary artery disease or symptoms. On examination he had a regular heart rate at 30/min with cannon waves in the neck veins. A grade II/VI systolic murmur was heard along the left sternal border. The ECG was highly variable, with at times normal sinus rhythm, 2:1 and 3:1 atrioventricular block and complete heart block. Conduction beyond the A-V node varied, including normal QRS, right bundle branch block (RBBB) with left inferior hemiblock, and left bundle branch block. Because of a history of pneumonia responding to penicillin 5 months earlier, a presumptive diagnosis of myocarditis was made and treatment with steroids begun. However, he returned one month later with near-syncopal attacks and complete heart block with a rate of 23/min, and a permanent demand pacemaker was implanted. Since that time he has done well on no medica-
tions, and intermittently overrides the pacemaker with normal sinus rhythm and left bundle branch block.

Additional data on this kindred reveals the following (see fig. 1): III-1 and III-2, brothers of J.S. (III-6), are reportedly healthy and have normal ECGs. III-5, sister of J.S., is reportedly healthy, and shows ECG abnormalities similar to those of her brother, i.e., wandering atrial pacemaker and rate varying from 47/min to 75/min. I-1, father of A.S. (II-1), was not known to have heart disease but died suddenly in his early 50s. Patients III-3 and III-4 have not been examined.

Discussion

Familial conduction defects have been well documented in the medical literature, with the available data ranging from pre-electrocardiographic clinical findings within an immediate family to studies involving over 250 members of a single kindred and His bundle electrogams, histopathology and intracardiac electrophysiology. The majority of affected individuals involved have shown onset of arrhythmias in the fourth decade of life or later, with progressive changes and conduction defects distal to the bundle of His, as well as bundle branch block.

In 13 of the reported kindreds, however, heart block was congenital. These cases were characterized by normal width and configuration of the QRS complex, absence of progressive changes, and where postmortem studies were obtained, pathologic changes at the His bundle or between it and the A-V node with no involvement of more distal conduction tissue. These data have led Sarachek and Leonard to postulate two types of familial heart block, the adult-onset and congenital types, differing both in etiology and in expression. They suggested that the mode of genetic transmission for both familial types is autosomal dominant with variable expressivity, although data in the congenital group have been felt by many authors to be inadequate for genetic analysis.

In a collaborative international study, Michaelson and Engle reported that 13 of 14 families with congenital complete heart block conformed to an autosomal recessive mode of inheritance. In two families there were three affected siblings.

Recently a newly recognized predisposing factor to congenital heart block has come to light: maternal connective tissue disease. Chameides et al. reported five children with congenital CHB born to four mothers with definite SLE, and three other questionable cases. Included in his report is one family with two affected siblings without other known conduction defects in the propositi or their relatives. McCue et al. reported 14 infants with congenital CHB of 11 mothers with clinical and/or serological evidence of connective tissue disease. Both authors suggest that maternal SLE may be contributing to a heretofore unrecognized degree to the population of patients with congenital CHB. In the latter study, in fact, 22 patients were screened to determine the 14 with this association, suggesting a large contribution from CTD.

We postulate that the "S" family represents the interaction of two predisposing factors: genetic (paternally transmitted conduction defects apparently of the adult-onset type) and environmental (maternal SLE), resulting in the birth of two infants with congenital CHB, which caused heart failure with severe hepatosplenicomegaly and thrombocytopenia. In the case of the second child, W.S., the presence of maternal SLE is definite and there is strong evidence of congenital SLE in this patient.

As the association was not looked for in the earlier case, T.S., one can only postulate the presence of subclinical SLE in the mother at that time. The negative ANA obtained on the mother following that pregnancy does not rule out that possibility, as serologic findings can vary widely for a given patient at different times in her obstetrical history. McCue suggests that the transplacental transmission of abnormal maternal antibodies suspected of damaging the fetal conduction system may occur "even prior to the development of clinical maternal SLE or CTD." Hogg, in 1957, reported a case of congenital SLE and CHB in an infant whose mother did not demonstrate findings of SLE until 11 months postpartum. In addition, this mother's medical history includes symptoms suggestive of CTD antedating both pregnancies by several years. The postmortem findings in T.S. (with the exception of meconium aspiration, the immediate cause of death) are markedly abnormal but nonspecific. They suggest severe intrauterine hypoplasplasmia, possibly secondary to congestive heart failure, and represent a more extreme case of the similar clinical findings which occurred in W.S. and also in a case reported by McCue. Unfortunately, neither conduction system dissection nor immunofluorescence were performed. The presence of subendocardial calcific deposits suggests an inflammatory process involving the conduction system, and we question whether the unusual epicardial pathology may also reflect a noninfectious inflammatory process, such as that seen in some cases of lupus pericarditis.

The importance of genetic-environmental interactions in the production of congenital heart disease has been recognized for some time. A similar interaction has been proposed in the etiology of adult-onset familial heart block, in which a genetic predisposition is manifested only in the presence of the normal subendocardial fibrosis of aging. We propose such an interaction in the production of congenital CHB in the "S" family. The environmental influence in this case is postulated to be the presence of abnormal maternal antibodies attacking a genetically vulnerable conduction system at a critical period in fetal development. The action of antibody as a primary teratogen has been suggested in the etiology of structural cardiac anomalies as well as congenital CHB.

Wallgren, in 1960, postulated the involvement of a maternal immunological response to explain the presence of congenital CHB in all three live births to one mother with no conduction defects in other generations. However, he dismissed this possibility as unlikely. A review of the reported kindreds with familial congenital CHB, excluding cases with associated intracardiac structural defects (table 1), reveals that 9 out of 14 such kindreds show multiple involvement among siblings without involvement in any other generation. Included is the family reported by Chameides et al. with definite maternal SLE, the families reported by McCue with definite maternal SLE, and that reported by Wright in 1959 where it is incidentally mentioned that the mother of the three affected siblings died of SLE. A fifth kindred, reported by Aylward in 1928 with electrocardiographic confirmation by Aitken in 1932, mentions the
presence of maternal Mikulicz's syndrome, now felt to belong to the spectrum of connective tissue diseases and frequently associated with SLE.21,19,28 This raises the question of whether the other four single-generation families were also victims of an ongoing environmental influence such as maternal SLE.

A review of the remaining five kindreds with multiple-generation involvement (including the "S" family reported here) reveals yet another pattern. All of the families show not only congenital CHB, but also other conduction defects (acquired CHB, RBBB, left anterior hemiblock, Wolff-Parkinson-White syndrome, wandering atrial pacemaker) usually associated with adult-onset type of familial block. These kindreds could have adult-onset type familial block with variable expressivity or diverse and progressive pathology following some initial insult.30,31 A unifying concept is that these families may represent a genetic-environmental interaction such as that seen in the "S" family.

A number of authors have observed the poor prognosis associated with the familial form of congenital CHB as opposed to the nonfamilial sporadic form.10,18 No explanation has been put forth for this discrepancy. If, however, this familial form does represent an immunological insult, one can postulate a prognosis worse than that in isolated idiopathic congenital CHB, based on evidence for involvement extending beyond a focal area of the conduction system. Certainly a portion of the isolated cases of congenital CHB also reflect maternal CTD, but a higher proportion of these cases would be seen in multiply-affected families. In addition, the very presence of multiple involvement in such families may reflect a more severe response to this immunological teratogen, producing greater morbidity and mortality in the affected individuals.

Acknowledgment

We would like to thank Dr. Antonio Martinez-Hernandez for his assistance in interpreting the pathological specimens in case 3.

### Table 1. Reported Cases of Familial Congenital Complete Heart Block

<table>
<thead>
<tr>
<th>Author</th>
<th>Number of affected sibs</th>
<th>Other affected relatives</th>
<th>Conduction defects other than CHB</th>
<th>Maternal CTD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aylward</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>SLE</td>
</tr>
<tr>
<td>Wright</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>SLE</td>
</tr>
<tr>
<td>Wallgren G</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>SLE</td>
</tr>
<tr>
<td>Lynch</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>SLE</td>
</tr>
<tr>
<td>Crittenden</td>
<td>4 (75)</td>
<td>0</td>
<td>0</td>
<td>SLE</td>
</tr>
<tr>
<td>James</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>SLE</td>
</tr>
<tr>
<td>Chamielides</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>SLE</td>
</tr>
<tr>
<td>McCue Case 2</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>SLE</td>
</tr>
<tr>
<td>Veracocheo</td>
<td>1</td>
<td>RBBB</td>
<td>0</td>
<td>SLE</td>
</tr>
<tr>
<td>&quot;S&quot; family</td>
<td>2</td>
<td>LAD, RBBB, LBBB, WAP, pacemaker</td>
<td>0</td>
<td>SLE</td>
</tr>
</tbody>
</table>

**Abbreviations:** CHB = complete heart block; CTD = connective tissue disease; SLE = systemic lupus erythematosus; RBBB = right bundle branch block; LBBB = left bundle branch block; WPW = Wolff-Parkinson-White syndrome; PAT = paroxysmal atrial tachycardia; WAP = wandering atrial pacemaker.

### References

UNUSUAL TRUNCUS ARTERIOSUS COMMUNIS/Angelini et al. 1107


Truncus Arteriosus Communis

Unusual Case Associated with Transposition

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SUMMARY A child with truncus arteriosus communis, characterized by the posterior origin of an individualized pulmonary trunk is presented. This relationship between the great arteries is unusual in truncus arteriosus communis and the spatial orientation resembles that seen in transposition of the great vessels. A brief discussion is proposed about a proper terminology in this type of complex anomaly.

VARIETIES OF COMMON TRUNCUS ARTERIOSUS have been previously discussed in the literature. For classification purposes, the length of the main pulmonary trunk and its origin from the common trunk have been most frequently utilized. It has been suggested that the type of common truncus, with a persisting segment of the pulmonary artery (type I of Collett and Edwards), is embryologically derived from the partial failure of completion of truncal septation.

Depending upon the length of the main pulmonary artery segment and its position with reference to the aortic portion of the common trunk, it might be possible to identify truncus arteriosus in which the aorta and pulmonary artery remnants are in the position usually identified as transposition of the great arteries. This type of great vessel arrangement has not been reported in truncus arteriosus.

The present case report is illustrative of what we believe to be the simultaneous presence of "common truncus" and transposition of the great vessels.

Case Report

A five-year-old child was admitted to Texas Children’s Hospital for evaluation of congenital heart disease. He was essentially asymptomatic, but known to have a complicated heart anomaly from previous venous angiographic study.

On physical examination the child was well developed and had no signs of congestive heart failure. The blood pressure was 90/60 in both arms. There was no evidence of mild cardiomegaly with a right ventricular heave palpable at the left lower parasternal area. A grade 2 systolic ejection murmur began immediately following an ejection click and was heard best in the pulmonary area. The second heart sound was single. No diastolic murmurs or sounds were heard. The electrocardiogram was interpreted as regular sinus rhythm with evidence of right ventricular hypertrophy (fig. 1). By X-ray examination, the heart was slightly enlarged, without selective chamber enlargement. The aortic arch was on the left side. The vascular pedicle was narrow. The pulmonary vascular shadows were large near the mediastinum, but small near the periphery of the lungs (fig. 2).

Heart catheterization data are presented in table 1.

A large ventricular septal defect was seen in the angiograms below a single overriding semilunar valve. A single arterial vessel of short length emerged from the heart and divided into two vessels; one with the characteristics of an ascending aorta and one with those of a pulmonary artery. The main pulmonary artery arose posteriorly from the common trunk and had a 2 cm long undivided segment that was obscured by the ascending aorta in the postero-anterior projection and was seen to be completely posterior to the aorta in the lateral projection (fig. 3).

The final diagnosis was trunco-conal septal defect (common truncus arteriosus) with transposition of the divided portion of the great vessels and pulmonary vascular obstructive disease.

In view of the high pulmonary resistances (ratio of pulmonary to systemic resistances equal to 0.78) this child was not considered a suitable candidate for corrective surgery.

Discussion

In most anatomic specimens of common truncus arteriosus, type I of Collett-Edwards, the longer the main pulmonary artery trunk, the more lateral and anterior is its...
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