Association of a Mosaic Chromosomal 22q11 Deletion With Hypoplastic Left Heart Syndrome

Michael W. Consevage, MD, PhD, James R. Seip, BS, Deborah A. Belchis, MD, Abby T. Davis, MD, Barry G. Baylen, MD, and Peter K. Rogan, PhD

Hemizygosity of chromosome 22q11 is a well-established cause of DiGeorge syndrome, velo-cardio-facial syndrome, isolated conotruncal congenital heart defects, and certain familial cardiac malformations. Most of these conditions are associated with deletion in band 22q11.2 and form a clinical spectrum of disease for which the acronym "CATCH 22" (cardiac defects, abnormal facies, thymic hypoplasia, cleft palate, hypocalcemia) has been proposed.[1] Less frequently, nonconotruncal defects may also occur in CATCH 22.[1–3] Consequently, the spectrum of congenital heart disease in this syndrome may be broader than previously recognized. Hypoplastic left heart syndrome has been associated with deletion of chromosome 22q11 in only 2 patients to date.[1] We present an infant with hypoplastic left heart syndrome, as well as facial anomalies characteristic of CATCH 22 syndrome, with a mosaic deletion of chromosomal 22q11 sequences.

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The female proband was the product of a full-term gestation and was born to a 32-year-old woman, gravida 2, para 1-0-0-1, with Apgar scores of 9 at 1 and 5 minutes. The pregnancy was uncomplicated, with no history of maternal illness or teratogen exposure. The birth weight was 2,711 g, length was 45 cm (5%),

From the Departments of Pediatrics and Pathology, College of Medicine, Pennsylvania State University, Hershey, Pennsylvania. This work was supported by a grant from the Central Pennsylvania Chapter of the March of Dimes Birth Defects Foundation (P.K.R.). Dr. Rogan's address is: Division of Genetics, Department of Pediatrics, Milton S. Hershey Medical Center, 500 University Drive, Hershey, Pennsylvania 17033. Manuscript received September 25, 1995; revised manuscript received and accepted November 30, 1995.

and head circumference was 31.5 cm (<5%). On the first day of life, the infant had a holosystolic murmur, tachypnea, and circumoral cyanosis and was transferred to our institution for further evaluation. The infant appeared ''wasted,'' mildly icteric, and disproportionately small for gestational age, and had findings of cardiorespiratory distress. Vital signs on admission were blood pressure 63/35 mm Hg (right arm), heart rate 160 beats/min, respiratory rate 80 to 90 breaths/min, and 93% oxygen saturation. Cardiovascular examination was remarkable for a loud first heart sound and a single second sound with a grade 3/6 holosystolic murmur. Chest x-ray demonstrated moderate cardiomegaly and increased pulmonary vascularity, and a ''small'' thymic shadow. Pertinent laboratory values included white blood cell count 10.2 with 12% bands, 59% neutrophils, and 27% lymphocytes; hematocrit 41.3%, and serology negative for rubella, toxoplasmosis, herpes, and cytomegalovirus. Parathyroid hormone levels were not measured; however, the ionized calcium ion levels were normal (1.03). Absolute T-cell subsets were normal.

A 2-dimensional echocardiogram demonstrated levocardia, atrial-ventricular and ventricular-arterial concordance, mitral and aortic valve atresia, hypoplastic left ventricle, patent foramen ovale, patent ductus arteriosus with bidirectional shunt, an inordinately hypoplastic ascending aorta with tubular hypoplasia of the transverse arch, and a single origin of the

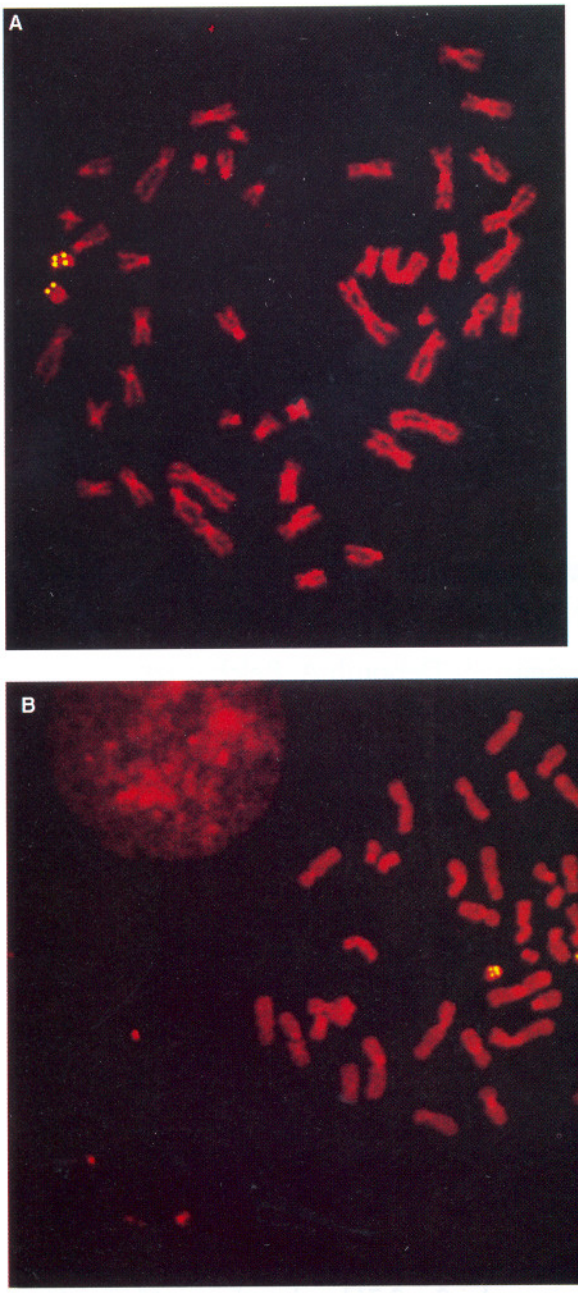

FIGURE 1. Representative leukocyte metaphase nuclei demonstrating a deletion of chromosome 22q11.2 (*A*) and a diploid constitution (*B*) at locus D22S75 in different cells from the proband. The control probe, D22S39 (22q13.3), is intact in both cell lines.

coronary arteries. These findings were consistent with a diagnosis of hypoplastic left heart syndrome.

The patient underwent a modified Norwood procedure on day 5 of life. She developed a low cardiac output state (with findings suggestive of myocardial ischemia and coronary artery insufficiency) and subsequently died of multisystem organ failure. Parental permission for a limited thoracic autopsy was granted.

A postmortem examination of the heart supported the echocardiographic findings and was consistent with hypoplastic left heart syndrome. The left ventricle was rudimentary with no outlet, both the aortic and mitral valve were atretic, and the left atrium was hypoplastic. The hypoplastic ascending aorta was surgically anastomosed to the pulmonary trunk, creating a common aortopulmonary trunk (Norwood stage I procedure). There was a single coronary ostium with a tortuous, dilated left coronary artery. A 4 mm impragraft from the right common carotid artery to the pulmonary artery was intact. The thymus was small ($1.0 \times 0.5 \times 0.5$ cm), consisting only of a cervical component and lacking a mediastinal one, and exhibited stress involution. Additional important findings were microcephaly, myocardial ischemia, and hyaline membrane disease. Because the autopsy permit was restricted, the parathyroids could not be examined.

A chromosomal abnormality was suspected because of her disproportionately small size for gestational age. CATCH 22 syndrome was considered in view of the facial abnormalities, the small thymic shadow on chest x-ray, and associated congenital heart disease.

The blood sample used in the following cytogenetic analysis was obtained from the patient on the second day of life (before transfusion). Fluorescence in situ hybridization (FISH) with a digoxigenin-labeled probe from 22q11.1 (D22S75) was performed according to the manufacturer's specifications (Oncor, Gaithersburg, Maryland). Simultaneous fluorescent detection of the diploid probe, D22S39, at 22q13.3 served as a positive control for the hybridization procedure. Thirty lymphocyte metaphase nuclei were examined by FISH. Five cells (16%) displayed a single copy of D22S75 (Figure 1A), whereas chromosomes from the remaining cells revealed 2 copies with this probe (Figure 1B). In all cells, D22S39 hybridized to both copies of chromosome 22. The presence of cells containing both normal and deleted chromosomes indicated that the patient was a somatic mosaic at D22S75. Cytogenetic analysis of mosaicism in postmortem heart tissue was not possible. Karyotypes and FISH analysis of leukocytes from both parents indicated a normal chromosomal constitution (results not shown), which is consistent with a postzygotic origin of the deletion in this patient.

One can speculate that the chromosomal deletion in this patient led to her atypical phenotype. Other explanations include the possibility that she harbored a unique chromosomal deletion or genetic background. Nevertheless, the mosaic genetic constitution may provide a plausible explanation for the constellation of abnormalities that were present.[4]

The atypical presentation of CATCH 22 raises several important concerns. First, in this patient, as in others, the heart defects were found in association with subtle facial abnormalities but with few of the other criteria normally seen in CATCH 22.[3] This association alone may be sufficient to raise suspicion that an interstitial 22q11 deletion may be present. Second, the incidence of chromosome 22 deletions in parents of children with a 22q11 deletion (25%) suggests that siblings or subsequent fetuses may also be at risk.[1] Parents with subtle or unusual manifestations of CATCH 22 may be unaware of their potential carrier status. Finally, the recognition of chromosomal mosaicism in this patient may have been fortuitous, as cytogenetic studies of leukocytes from other individuals with a mosaic karyotype may sometimes fail to reveal a 22q11 deletion that is present in cardiac tissues. Molecular cytogenetic analysis of cardiac specimens that are removed during routine surgical procedures may be warranted in appropriate clinical situations.

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