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Aortic Root Dilatation Associated with Partial Trisomy 7(q31.2→qter)

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SUMMARY. **Aortic root dilatation and mitral valve prolapse are cardiac findings sometimes seen in disorders of connective tissue, most often in the Marfan syndrome. This report describes an infant with these cardiac anomalies and a specific chromosomal abnormality, partial trisomy of chromosome 7 associated with partial monosomy of chromosome 22. This association may have significance with respect to the etiology of cardiac disease in connective tissue disorders such as Marfan syndrome.**

KEY WORDS: **Marfan syndrome — Aortic root dilatation — Trisomy 7**

Aortic root dilatation in children is most commonly seen in patients with the Marfan syndrome, a heritable disorder of connective tissue transmitted as an autosomal dominant trait. Despite the long history of recognition of this syndrome, a specific chromosomal marker has not been linked with it. The gene coding for type-I collagen has been located on chromosome 7, suggesting that this or other connective tissue diseases may be linked to abnormalities of this chromosome [4, 6, 9]. We describe an infant with both aortic root dilatation and mitral valve prolapse, which are typical marfanoid cardiac findings, associated with the karyotype 46 XY, −22, +der(22), t(7;22)(q31.2;q13)pat. He also had other features suggestive of a connective tissue disorder such as the Marfan syndrome, as well as additional congenital anomalies not usually associated with this phenotype.

Case Report

This 2450-g infant male product of a twin gestation at 35 weeks to a 30-year-old gravida-5 para-1 black woman was born by caesarean section following a pregnancy complicated by the infant's discordant head size. The patient was noted to have a head size of 36.75 cm (>90th percentile for gestational age), as well as multiple congenital anomalies, including low-set ears, large feet and hands with arachnodactyly and camptodactyly, contractures of the thumb joints, a broad chest, a sacral dimple, and bilateral inquinal hernias. Computed tomography of his head demonstrated ventriculomegaly with patency of the fourth ventricle, megencephaly, cavum septum pellucidum, and encephalomalacia. Abdominal ultrasound revealed absence of the right kidney. A chest radiograph showed abnormalities of the vertebral bodies of T4 and T8 and absence of the 12th rib. Notably, his female twin had no abnormalities.

On day 3 of life, a systolic ejection murmur along the upper left sternal border was noted. The first and second heart sounds, as well as the pulses, were normal. There was no click or diastolic murmur. Chest roentgenogram showed normal cardiac contours and pulmonary vascular markings. Electrocardiophic findings were within normal limits. Echocardiography demonstrated a patent ductus arteriosus and an aortic root dimension of 11 mm (Fig. 1A), with the upper limit of normal being 12 mm [5].

Because of the multiple abnormalities, chromosomal studies were performed. Peripheral blood lymphocytes from the patient, his twin sister, and both parents were cultured for chromosome analysis with trypsin-G banding. The mother and twin sister were found to have normal karyotypes. The patient's father was found to have a reciprocal balanced translocation involving the long arms of chromosomes 7 and 22. The break point in chromosome 7 was q31.2, and the breakpoint was q13 in chromosome 22. Thus, the karyotypes were interpreted as 46, XY, t(7;22)(q31.2;q13). The patient was found to have a chromosome number of 46, with an abnormal chromosome 22 inherited from his father. The patient's karyoptypes were interpreted as 46, XY, −22, +der(22), t(7;22)(q31.2;q13)pat, making him partially trisomic for the long arm of 7(7q31.2→qter). Other members of the father's family were not studied.

The patient was readmitted for repair of an omphalomesenteric duct cyst at 1 month of age, placement of ventriculoperitoneal shunt at 5 months, and treatment of bacterial sepsis at 11 months. He also manifested a coagulopathy diagnosed as hemo-

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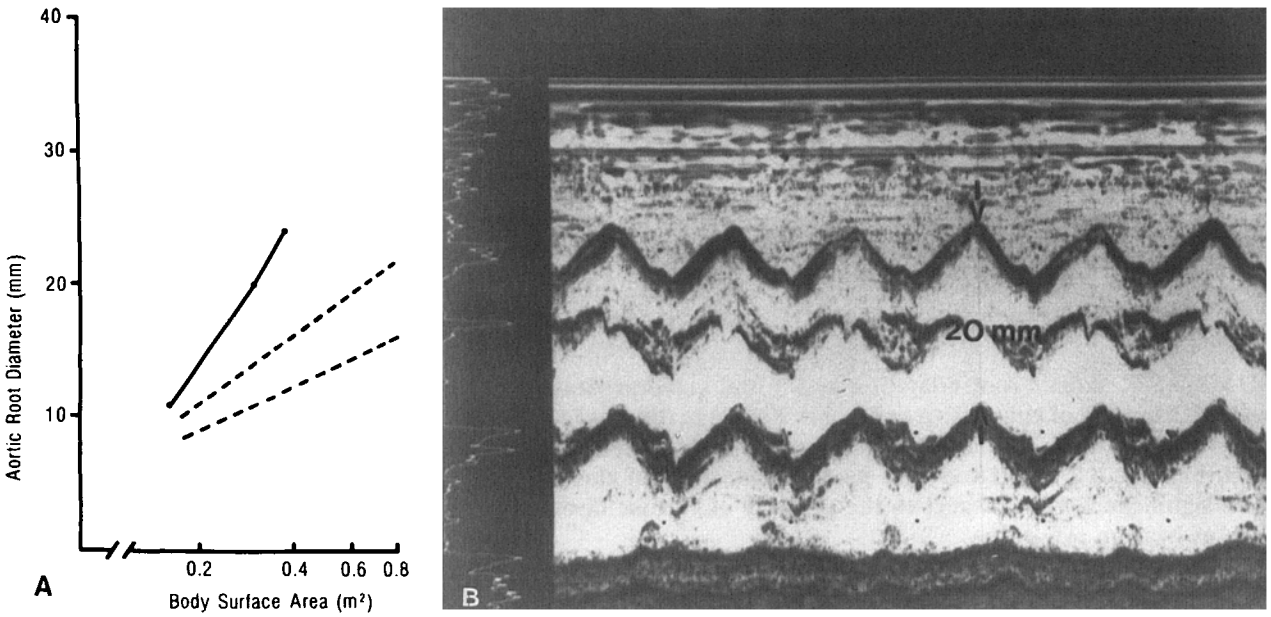

Fig. 1 **(A)** Plot of aortic root diameter (millimeters) versus a cube root function of body surface area (square meters). The *dashed lines* indicate the 95% confidence limits for normal children (after Sisk et al. [11]). The *solid line* represents serial aortic measurements in our patient. **(B)** M-mode echocardiograph of the patient's aortic root at 5 months of age. This corresponds to the second measurement in **A.**

philia C (factor-XI deficiency). Ophthalmologic examinations revealed strabismus, but no abnormalities of the lens.

The patient's cardiac status was reassessed during each of these subsequent admissions, using chest roentgenograms, clinical examination, and echocardiography. The patient ductus arteriosus closed. At 5 months and 11 months of age, progressive dilatation of the aortic root to 20 mm and 24 mm, respectively, was noted by two-dimensional and M-mode echocardiographic examination (Fig. 1A and B). Normal aortic root size is up to 13.5 mm at both ages [5]. Doppler evaluation consistently showed no aortic insufficiency. In addition, the patient demonstrated mild mitral valve prolapse. The patient's parents and twin sibling were evaluated and all had aortic root dimensions within the normal range, and none had physical features suggestive of the Marfan phenotype or other connective tissue disorder.

Discussion

Partial trisomy of the long arm of chromosome 7 has been reported by several authors, and was recently reviewed by Couzin et al. [2]. Our patient has partial trisomy for the segment 7q31→qter, an abnormality reported in five cases in Couzin's review. Important clinical features of the 7q31→qter trisomy are low birth weight; growth and mental retardation; low-set, abnormal ears; cleft palate; micrognathia; large tongue; wide anterior fontanel; skeletal abnormalities; and early death. Congenital heart defects were reported in two cases, but did not include aortic root dilatation. Our patient also has a partial monosomy 22. This defect has been associated with the DiGeorge syndrome [3, 7]. Patients with DiGeorge sydnrome commonly have abnormalities of the great arteries, but also do not have isolated aortic root dilatation. Further, the syndrome appears to reflect a deletion of 22 q11, a band that is still present in our patient.

The diagnosis of Marfan syndrome is usually based on four criteria: familial occurrence, cardiovascular abnormalities (especially aortic root dilatation), ocular changes, and skeletal features, and is reviewed elsewhere [10]. Our patient's aortic root became very enlarged for his body surface area (Fig. 1A) [5], and his aortic root diameter is easily within the range typical of Marfan syndrome, i.e., more than 50% greater than the upper limit of normal [10, 11]. Very few other conditions, including other defined disorders of connective tissue, involve this degree of aortic root enlargement in early childhood in the absence of significant aortic insufficiency. The patient's arachnodactyly, long feet and hands, and inquinal hernias are also characteristics of connective tissue disorders including the Marfan syndrome. Mitral valve prolapse is also consistent with the diagnosis, although not specific for it. Measurements of the patient's length versus arm span (they are equal) are complicated by his severe hydrocephalus with cranial enlargement. Moreover, this patient has several features not typical of the Marfan phenotype, including his central nervous system abnormalities and absent right kidney.

The basic connective tissue defect leading to the pleiomorphic phenotypic outcome of Marfan syndrome has not been agreed upon. Research to date has focused on type-I collagen. Collagen biosynthesis has been implicated through the study of an abnormal tissue cell culture from a patient with the Marfan syndrome [1]. This link to collagen has led to the postulate that chromosome 7 may carry the defect [6, 9], because a precursor to type-I collagen has been shown to be a product of this chromosome in molecular hybridization studies [4]. Furthermore, disturbances in collagen biosynthesis have been noted in cell cultures from spontaneously aborted embryos having trisomy 7 [8]. Mechanisms that might account for these findings would include a dosage effect suggested by the embryonic cultures, although mutation or position effects would appear more likely in the case of the Marfan patient. Other studies have indicated that the gene for Marfan syndrome does not lie on chromosome 7, and the fibrillin rather than collagen is the structural protein affected in Marfan patients (R.E. Pyeritz, personal communication, 1988). The possibility that the Marfan phenotype results from heterogeneous abnormalities of connective tissue cannot be excluded at present.

We believe this is the first report of a patient with aortic root dilatation and mitral valve prolapse, cardiac findings most often found in patients with the Marfan syndrome, associated with a known chromosomal defect. As such, this case may represent a clue to the possible origin of structural changes seen in patients with connective tissue disorders such as Marfan syndrome.

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