FETAL RHABDOMYOMA: PRENATAL DIAGNOSIS, CLINICAL OUTCOME, AND INCIDENCE OF ASSOCIATED TUBEROUS SCLEROSIS COMPLEX

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Objectives We reviewed our institution's experience with fetal cardiac rhabdomyoma to document the clinical outcome and incidence of associated tuberous sclerosis complex (TSC) and compared our findings with those of patients diagnosed with cardiac rhabdomyoma after birth.

Study design We reviewed the medical records of all cases diagnosed prenatally and postnatally with cardiac rhabdomyoma between January 1990 and June 2002.

Results Twenty fetuses with cardiac rhabdomyoma were diagnosed at 28.4 ± 6.0 weeks' gestational age. Of 19 continued pregnancies, there was one spontaneous intrauterine death, and 18 were delivered at term. Although none had prenatal hemodynamic complications, after birth seven had cardiac symptoms requiring medical (n = 4) or surgical intervention (n = 3). On follow-up, 15 of 19 with available outcome had TSC (79%), including six with neurodevelopmental disease. Over the same period, 26 patients were diagnosed with cardiac rhabdomyoma postnatally. Most (77%) were referred for cardiac assessment after findings suggesting TSC. On follow-up, TSC was confirmed in 25 (96%), including 22 with neurodevelopmental disease. The incidence of cardiac symptoms and TSC was not statistically different between the prenatal and postnatal diagnosis groups.

Conclusions Cardiac rhabdomyomas are benign from the cardiovascular standpoint in most affected fetuses. As observed in postnatally diagnosed cardiac rhabdomyoma, TSC is diagnosed in most cases of fetal cardiac rhabdomyoma. *(J Pediatr 2003;143:620-4)*

Primary cardiac tumors are rare, with an estimated incidence of 0.27% among pediatric autopsies.[1] The most common type of cardiac tumor identified in infancy and childhood is rhabdomyoma.[1] Postnatal diagnosis of cardiac rhabdomyoma (CR) is often made when signs and symptoms of tuberous sclerosis complex (TSC) are identified,[2-5] or when there is a family history prompting cardiac assessment as part of the clinical work-up. Only occasionally does a patient present with cardiac symptoms that necessitate medical or surgical intervention. Because many affected infants have no cardiac symptoms, CRs not associated with TSC may go unrecognised. Therefore, the true incidence of CR in infants and children and the frequency of the associated TSC in all affected infants remain unclear.

As is true after birth, CRs are by far the most common cardiac tumor diagnosed in utero.[6] In contrast, however, the prenatal diagnosis of CR most often occurs after referral for the finding of a cardiac tumor or fetal dysrhythmia on routine obstetrical ultrasound assessment without other obvious features of TSC at the time of diagnosis. Knowledge of the outcome of affected fetuses and the true incidence of TSC in fetal CR is critical for accurate prenatal counseling and planning of prenatal treatment. In the current study, we reviewed our institution's experience with fetal CR encountered over a 12-year period to document the diagnosis, clinical outcome, and incidence of TSC in affected fetuses. We compared our findings with those of infants and children diagnosed with CR only after birth over the same period. We hypothesized that patients diagnosed before birth with CR

CR	Cardiac rhabdomyoma	TSC	Tuberous sclerosis complex

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represent a less biased population than those presenting after birth with a lower incidence of TSC.

METHODS

We identified all cases diagnosed prenatally and postnatally with CR between January 1990 to June 2002 by using the computer database in the Division of Cardiology at the Hospital for Sick Children. For the cases diagnosed prenatally, we reviewed the obstetrical charts and the results of the fetal echocardiography and detailed fetal ultrasound, as well as the postnatal records, including the genetic, surgical, and pathology records of the patients. For the cases detected postnatally, the pediatric records were reviewed. The following were documented for the cases diagnosed prenatally: the results of the fetal echocardiographic assessment; the mother's age at referral; the gestational age at the time of referral; family history of TSC, including a thorough parental physical examination and Wood's lamp skin examination; the tumor location, number, size, and hemodynamic effect; the presence of fetal arrhythmia and need for maternal antiarrhythmic therapy to control fetal arrhythmia; delivery mode; infant's sex, birth weight, and Apgar score; and postnatal clinical course, including intermediate and late follow-up for cardiac symptoms, tumor size, seizure, and developmental delay. A histologic diagnosis was recorded when available. For the patients diagnosed with CR after birth, the following data were collected: indication for cardiac assessment; age at diagnosis of CR; the presence of cardiac symptomatology or need for cardiac medication; history of seizures; obvious developmental delay or behavioral changes; family history of TSC, including a thorough parental physical examination and Wood's lamp skin examination; and the tumor location, number, and hemodynamic effect.

The diagnosis of TSC was based on the criteria established at the 1998 Tuberous Sclerosis Complex Consensus Conference.[7] Because most of the criteria cannot be diagnosed prenatally, we based the prenatal diagnosis of TSC in our study on the detection of two major criteria detectable prenatally: CR and cerebral tumors detected on fetal ultrasound or magnetic resonance imaging of the brain or both.

This retrospective study was approved by the Research Ethics Board of the Hospital for Sick Children.

Statistical Analysis

All values such as mother's age, gestational age at diagnosis, number of tumors in a cardiac chamber, and follow-up period were expressed as mean ± SD, median, and range. All other variables were expressed as frequencies. The other variables between the two groups were evaluated by using χ^2 analysis.

RESULTS

In the study period, 1020 fetuses were diagnosed at our center with functional heart disease, structural heart disease, or dysrhythmias. Of these, 20 fetuses (2%) had a diagnosis of CR. The reasons for referral for fetal cardiac assessment were routine obstetric ultrasound suggesting a cardiac mass (n = 15), maternal diabetes (n = 2), fetal arrhythmia (n = 2), and family history of tuberous sclerosis (n = 1). Family history of TSC in a first-degree relative was positive in one (sibling) and probable in three other patients in whom the diagnosis in the relative was confirmed only after the finding of the fetal cardiac tumor. The mothers' mean age at pregnancy was 31.6 ± 4 years (median, 29.8). The mean gestational age at diagnosis was 28.4 ± 6.0 weeks; median, 28 (range, 19-37).

Clinical Outcome

Of the 20 cases detected prenatally, one had termination of pregnancy. Another case died in utero at 28 weeks' gestational age. Eighteen other mothers continued to term. Thirteen infants were born with spontaneous vaginal delivery, and five required cesarean section (two for maternal indications and three for fetal cardiac tumor diagnosed before 1995). The average weight was 3.4 ± 0.28 kg (median, 3.5 kg), and the median Apgar scores were 8 and 9 at 1 and 5 minutes, respectively. There were nine girls (50%) and nine boys (50 %). Duration of postnatal follow-up ranged from 6 weeks to 11 years (median, 2.9 years; mean, 3.8 ± 3.3 years). There have been no deaths in the 18 cases delivered and followed postnatally.

Cardiovascular Findings

At the initial diagnosis, there was a single tumor in two cases, and there were multiple tumors in 18 of the fetuses (Fig 1). Multiple tumors were located in the left ventricular free wall and the left ventricular side of the interventricular septum in 17, in the right ventricular free wall and the right ventricular side of the interventricular septum in 14, and in the right atrium in four. Tumor size ranged from 0.3 cm × 0.4 cm to 5 cm × 3.2 cm. Pathologic diagnosis of rhabdomyoma was made in five patients (two autopsy reports and three surgical specimens).

None of the 20 fetuses had prenatal evidence of cardiovascular compromise or hydrops fetalis. Nine of the 20 fetuses (45%) had dysrhythmias (persistent premature atrial or ventricular beats, supraventricular tachycardia, or persistent sinus bradycardia) initially observed at presentation. One mother required antiarrhythmic therapy in the form of Digoxin to control the fetal supraventricular tachycardia.

After birth, 10 infants had an abnormal initial electrocardiogram, including nine with dysrhythmias that were similar to those observed before birth. Of the 18 infants, seven had cardiac symptoms that necessitated therapy: one required medical therapy for heart failure (case 16), three required therapy for supraventricular tachycardia (cases 4, 14, and 15), and three required surgical resection of tumor or tumors (cases 6, 11, and 16) for severe left ventricular outflow tract obstruction.

At the time of the study, 16 of 18 patients available for assessment beyond the neonatal period were asymptomatic from the cardiac standpoint. Tumors spontaneously regressed

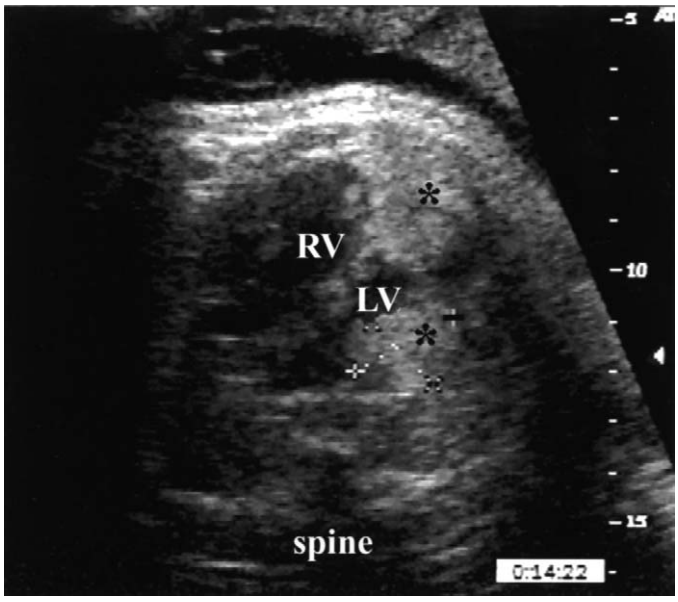

Fig 1. Four-chamber view obtained for fetus at 37 weeks' gestational age with multiple large CRs within the right (RV) and left (LV) ventricles (arrows).

(completely or partially) in 10 and remained unchanged in five. In one case, the tumor progressed in utero in the third trimester and required surgical intervention after birth.

Development of Tuberous Sclerosis Complex

Of 19 fetuses with CR and either postnatal follow-up (n = 18) or fetal autopsy (n = 1), 15 (79%) were diagnosed with TSC. Of the 15 cases, five (33%) had an abnormal fetal brain scan that revealed ventriculomegaly (caused by possible obstruction by cerebral tumor), cerebral astrocytoma (diagnosed by ultrasound), and subependymal nodules as well as cortical tumors (diagnosed by magnetic resonance imaging) suggestive of TSC. In postnatal follow-up, 10 of the 14 infants had cerebral pathology consistent with TSC based on magnetic resonance images or computer tomograms (Fig 2). Neurodevelopmental complications were present in six of 14 with a history of seizures and developmental delay. Skin involvement including hypomelanotic macules, shagreen patch, and facial angiofibroma was documented in eight patients.

Multiple CRs were seen in all 15 patients diagnosed with TSC. In the two patients with single CR, one did not develop TSC by 6 years of age, whereas the other is a neonate with no signs of TSC to date.

Postnatal Referral for Cardiac Rhabdomyoma

In the same study period, 26 patients were diagnosed postnatally in our institution with CR. The mean age at diagnosis of CR was 2.9 years (±4.2); median, 0.8 (range, 1 day to 14.8 years). The most common indication for cardiac assessment was suspected or confirmed TSC (n = 20). Other indications for echocardiography included cardiac symptoms observed in six (23%), including five with severe outflow obstruction and one with arrhythmia. There were 19 boys (73%) and seven girls (27%). All with cardiac symptoms presented at <6 months of age.

Tumors at diagnosis were single in five patients (19%), involving either the right or left ventricle, and multiple in 21 patients (80.8 %). All five with severe outflow tract obstruction required surgical resection of the tumor. At follow-up, five of these six patients were asymptomatic, and one had moderate aortic regurgitation after tumor resection. All other patients remained asymptomatic from a cardiovascular standpoint at a mean follow-up of 4.1 ± 2.5 years (median, 3.8 years). The tumors regressed (either partially or completely) in 25 (96%) and progressed mildly in one (4%) without causing any hemodynamic effect. All 26 patients are alive.

At follow-up, 25 of 26 patients with a postnatal diagnosis of CR (96 %) have a diagnosis of TSC, including all of the five with single tumors. Of the 26 patients, 19 (73%) developed seizures, 14 (53.8 %) had developmental delay, and three (12 %) had behavioral changes.

The difference in the incidence of cardiac symptomatology and diagnosis of TSC between the group diagnosed with CR prenatally and the one diagnosed postnatally was not statistically significant. The incidence of neurodevelopmental pathology, however, was significantly higher in the postnatal diagnosis group (P = .007.)

DISCUSSION

The prenatal diagnosis of CR was first reported by De Vore et al in 1982.[8] Several other reports followed describing isolated cases.[3,9] Only one previous series[6] reported the experience of several institutions with the diagnosis and outcome of cardiac tumors detected prenatally; 17 of 19 tumors were suspected CRs. Our study is the first to document the diagnosis and clinical outcome of a large group of affected fetuses with CR encountered in a single institution. Furthermore, our series documents in detail the incidence of TSC associated with fetal CR and the neurodevelopmental complications. We also compared these findings with infants and children who presented with CR postnatally.

As observed in our study, fetal CR is typically identified in the midtrimester. From our experience and the multicenter experience of Holley et al,[6] CRs are typically well tolerated, with a risk of only 4% to 6% of fetal demise. Dysrhythmias may be observed in 16%[6] to as high as 47% of cases, as observed in our series, and may necessitate prenatal or postnatal medical therapy. The natural history of most tumors detected prenatally is favorable, with most tumors regressing beyond the third trimester[6,10,11]; however, in rare cases, there may be progression in utero, as we and others had observed.[12] After birth, large tumors may affect the cardiac output, necessitating surgical resection or anticongestive medication, which occurred in four (22%) live-born infants in our series. The majority of cases, however, have a benign perinatal course,

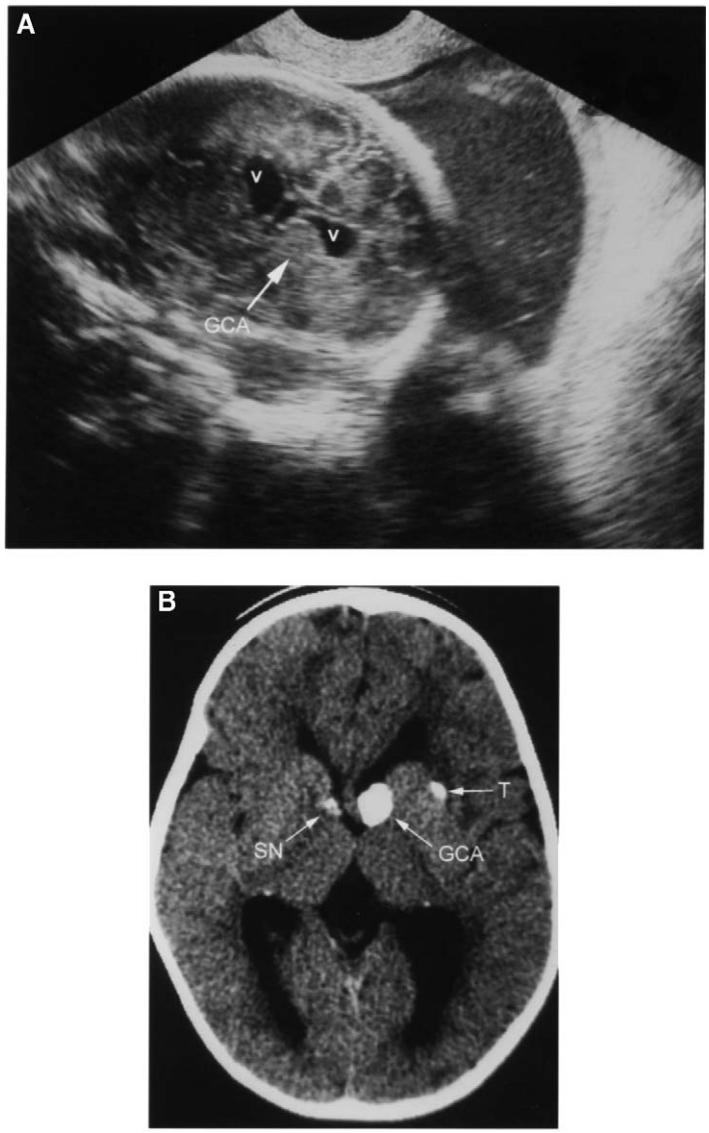

Fig 2. (A) Prenatal ultrasound of fetal brain at 30 weeks' gestational age in coronal plane through the anterior fontanelle. The anterior horns of the lateral ventricles (V) are dilated. There is an abnormal mass (giant cell astrocytoma, GCA) arising from the caudate nucleus area and indenting the ventricle close to the Monro foramen. (B) Axial computed tomography scan at age 24 months confirms the mass, which was shown to be a GCA by the Monro foramen. Additional lesions are also visible (*SN*, subependymal nodule; *T*, insular tuber). All the masses show calcification at this time.

with delivery at term, continued regression in size, and even complete resolution of more than 80% of the tumors within infancy and early childhood,[13] and no major neonatal and postnatal cardiac complications, a finding also in keeping with our observations in patients presenting after birth.

Tuberous Sclerosis Complex in Fetal Cardiac Rhabdomyoma

Tuberous sclerosis complex is an autosomal dominant multisystemic disorder with variable expressivity.[14] The population frequency is 1:10,000 to 1:6000,[9] and about 80% are caused by de novo mutation.[7,14] The association between cardiac CR and TSC is well known.[3–5] New diagnostic criteria for TSC were established in 1992[15] and revised in 1998.[7] In the revised consensus, family history of TSC, which has been used in previous reports of CR, was not included among the criteria. A close relative with TSC is an important clue for considering the diagnosis. However, basing the diagnosis on family history amounted to circular reasoning, because the positive family history is often the reason that the person is tested. Moreover, most patients with TSC have sufficient physical or radiographic findings to substantiate the diagnosis even without considering the family history. The diagnostic criteria for TSC and other findings are also age-dependent. Multiple CRs detected prenatally or in early infancy are no longer sufficient to establish the diagnosis of TSC.[7,15]

By using the strict criteria for the diagnosis of TSC revised in 1998, we found TSC in the majority of our cases of fetal CR. We have demonstrated a higher incidence in the

fetal group (79%) compared with the previously documented multicenter experience of antenatally diagnosed CR[6] and previous reviews of the literature of antenatally diagnosed CR,[3,5,13,16] which indicated an association of 50% to 58% with TSC.

When we compared our fetal experience with our institution's experience of postnatally diagnosed CR, no significant difference in the association with TSC was detected. Thus, the majority of prenatally and postnatally diagnosed CRs are associated with long-term development of TSC. The discrepancy between the incidence of TSC among prenatal cases detected with CR as observed in the current series in comparison with other series is probably the result of the longer follow-up of these patients and aggressive cerebral assessment by using various fetal and neonatal imaging modalities in our center.

Although the incidence of TSC in fetal CR does not statistically differ from that of the postnatal diagnosis group, we observed a decreased incidence of neurodevelopmental pathology in the fetal group compared with the postnatal group. We found seizures, developmental delay, or both in 43% of the prenatal diagnosis group compared with 88% of the group with postnatal diagnosis of CR. Given the indication for referral for fetal echocardiography (incidental finding of cardiac pathology on routine ultrasound) and our use of cerebral pathology identified by using head imaging modalities in the diagnostic criteria, it is possible that we are identifying a less severe spectrum of TSC in the prenatally diagnosed. The prenatal cases may be less severe because they are not biased in their presentation. However, our observed differences between prenatal and postnatal diagnosis group may also reflect differences in age at presentation and length of follow-up.

Finally, it has been suggested that fetuses with a single CR are at lower risk for the development of TSC.[17] In our series of CR, there were seven cases with single tumors. All five with a postnatal presentation had a diagnosis of TSC. Of the two with a prenatal diagnosis of CR, only one has follow-up beyond the neonatal period (current age, 6 years). In the series of Holley et al,[6] two of nine isolated tumors were associated with TSC, which could support a lower risk for developing TSC in cases with a single cardiac tumor. However, given the lack of histologic evidence of rhabdomyoma, the diagnosis of CR could not be confirmed.

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