Cardiac rhabdomyoma in intrauterine life: clinical features and natural history. A case series and review of published reports

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Cardiac rhabdomyoma; Fetal echocardiography.

Background. **Fetal cardiac rhabdomyoma is very rare; despite the fact that many cases and series have been reported, the clinical presentation, the natural history and the frequency with which this pathology is associated with tuberous sclerosis complex are not well determined. The aim of this investigation was to study the clinical features and the natural history of cardiac rhabdomyoma when diagnosed during prenatal life.**

Methods. **Nine cases of cardiac rhabdomyoma detected among 5276 fetal echocardiograms recorded over a 10-year period in a single center were retrospectively reviewed. Medical records and echocardiograms were studied to determine the prenatal and postnatal course and outcome.**

Results. **The incidence of cardiac rhabdomyoma in our center was 0.17%. The gestational age at diagnosis ranged from 27 to 36 weeks. The most common reason for fetal echocardiography was an abnormal obstetric ultrasound scan (6/9 cases). In no case was there a family history of tuberous sclerosis. In one case, the tumor was single whereas in 8 cases multiple tumors were diagnosed. During prenatal life the majority of tumors were clinically silent. One fetus died of hydrops and arrhythmia. Four children presented with arrhythmia postnatally and one required surgery. At a mean follow-up of 47 months, total or partial regression was observed in 7 patients. Seven patients developed postnatal clinical signs of tuberous sclerosis.**

Conclusions. **Fetal cardiac rhabdomyomas are often benign and have a tendency to regress, but their prognosis is guarded due to very frequent association with arrhythmias and tuberous sclerosis. During prenatal counseling, it is of utmost importance to inform the future parents of the virtually constant perspective of tuberous sclerosis complex.**

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Introduction

Primary heart tumors are very rare in all age groups. Among children presenting to pediatric cardiac referral centers, the incidence of cardiac tumors is reported to range between 0.08% (pre-echocardiography data)[1] and 0.20% (echocardiographic diagnosis)[2]. The most common primary tumor of the heart in infants and children is the rhabdomyoma, which represents 36-42% of tumors in autopsy series[3-5] and 79% in clinical series[2]. Among fetuses undergoing second or third trimester ultrasound evaluation, the incidence rates for tumors of the heart and pericardium are reported to range between 0.009% for a mixed low- and high-risk population[6] and 0.2% for a referral center[7]. The first case report of a rhabdomyoma diagnosed during intrauterine life by means of echocardiography was published in 1982[8]. Since then, many reports of isolated or few cases with particular features have appeared in the literature. In these reports, the authors frequently describe dysrhythmias[9-14], fetal hydrops[15,16], fetal or neonatal death[17,18] and termination of pregnancy[19,20]. The case series of fetal rhabdomyomas[7,21-26] shows diverse outcomes, ranging from spontaneous regression to fetal or neonatal death. The purpose of this retrospective study was to present our experience with cardiac rhabdomyomas diagnosed during intrauterine life and to discuss their clinical features and natural history with reference to the pertinent literature.

Methods

Among 5276 consecutive fetal transabdominal echocardiograms performed at our Institution between January 1991 and December 2000, 9 fetuses with single or multiple cardiac rhabdomyomas were identified. The diagnosis of cardiac rhabdomyoma was established in accordance with previously published criteria by Roach et

al.[27]. We would like to specify that ours was a low-risk population. In fact, almost 70% of scans were performed for routine ultrasound evaluation. Subjects were scanned using a Hewlett-Packard 77020A (Hewlett-Packard, Palo Alto, CA, USA) and an Acuson Aspen (Siemens Ultrasound, Mountain View, CA, USA) equipped with 3-7 MHz sectorial phased array probes, color Doppler facilities and videotape recording for later examination. The following data were collected for each subject: gestational age, reason for referral, family history of tuberous sclerosis, tumor number, size and location, clinical features, and outcome.

Results

The incidence of cardiac rhabdomyoma in our center was 0.17%, very similar to that reported in a multicenter experience[23]. The gestational age at the time of diagnosis ranged from 27 to 36 weeks with a mean of 32.2 weeks (Table I). The most common reason for fetal echocardiography was an abnormal obstetric ultrasound scan (6/9 cases). In the remaining fetuses, the indication for referral was arrhythmia in 2 and nonimmune hydrops associated with arrhythmia in 1. In no case was there a family history of tuberous sclerosis. The tumor was single in 1 fetus whereas in 8 multiple tumors were identified. The tumor size ranged from 2 to 22 mm. The tumors were located in the interventricular septum with or without other locations. In case 1, fetal echocardiography showed multiple cardiac tumors, one of them partially obstructing the left ventricular outflow tract. In case 2, one single large tumor localized in the interventricular septum caused significant mitral regurgitation and mild subaortic stenosis. The majority of tumors were clinically silent during fetal life. Case 6, which presented at 27 weeks of gestation with fetoplacentar nonimmune hydrops and frequent supraventricular extrasystoles, showed a large tumor localized in the interventricular septum and causing subaortic stenosis and a smaller mass in the roof of the right atrium. This fetus died at 28 weeks of gestation but necropsy was not performed. Case 7, examined at 36 weeks of gestation, presented with supraventricular paroxysmal tachycardia and multiple rhabdomyomas. In case 9, fetal echocardiography showed multiple small cardiac tumors and frequent supraventricular extrasystoles. The duration of postnatal follow-up ranged from 4 to 134 months (mean 47 months). Seven patients are alive with total (1 case) or partial (6 cases) regression of the tumor. In case 2, the large septal tumor and its associated hemodynamic lesions (mitral insufficiency and subaortic stenosis) did not regress and the patient was operated upon in another institution when he was 3 years old. Unfortunately, he died of intractable heart failure 6 months after surgery. The infant with supraventricular paroxysmal tachycardia and multiple tumors on the prenatal ultrasound (case 7) presented again with this arrhythmia after birth and was successfully treated with propafenon and digoxin. After birth, the fetus with extrasystoles (case 9) presented again with supraventricular extrasystoles. Two patients developed arrhythmias during the first month of life: case 3 showed supraventricular and ventricular extrasystoles and case 4 showed supraventricular extrasystoles and multiple and complex ventricular extrasystoles. It is remarkable that all 3 patients with an atrial localization of tumors had supraventricular arrhythmias. Tuberous sclerosis was clinically evident in 7 cases. Case 9, with the shortest lasting postnatal follow-up, did not have clinical signs of tuberous sclerosis. Case 5 presented with systemic hypertension associated with polycystic kidney disease.

Discussion

Cardiac rhabdomyomas are benign tumors composed of altered myocytes with large vacuoles and considerable quantities of glycogen (spider cells). They are considered to be hamartomas of striated

Table I. Patient characteristics and outcome.

Case	Sex	Follow-up (months)	Presentation	No. tumors and location				Hemodynamics	Regression	Status
				IVS	LV	RV	RA			
1	M	134	Abnormal, 4 chambers	2	1	3		Subaortic stenosis	Total	Alive, TSC
2	M	37	Abnormal, 4 chambers	1				Mitral insufficiency, subaortic stenosis	No	Died postop., TSC
3	M	58	Abnormal, 4 chambers	1	2	3			Partial	Alive, arrhythmias, TSC
4	F	54	Abnormal, 4 chambers	1		2	1		Partial	Alive, arrhythmias, TSC
5	F	41	Abnormal, 4 chambers	1	1				Partial	Alive, hypertension, TSC
6	M	–	Hydrops, arrhythmias	1			1	Subaortic stenosis	–	Fetal demise
7	M	26	Arrhythmias	2	2	1			Partial	Alive, arrhythmias, TSC
8	M	22	Abnormal, 4 chambers	1	1	2			Partial	Alive, TSC
9	F	4	Arrhythmias	1	2	2	1		Partial	Alive, arrhythmias

IVS = interventricular septum; LV = left ventricle; RA = right atrium; RV = right ventricle; TSC = tuberous sclerosis complex.

muscular fibers occurring exclusively in the heart. They are usually multiple, spherical in shape and range from 1 mm to 10 cm in diameter. Their most frequent localization is within the ventricles, especially in the interventricular septum, but they may also be found in the atria, at the cavoatrial junction[28] and exceptionally in the pulmonary trunk[29]. Well known is their association with the neurocutaneous syndrome, the so-called tuberous sclerosis complex[29-34]. The clinical presentation and the evolution of cardiac rhabdomyomas in children and adults are well known. Generally, the morbidity related to these cardiac tumors is low. In adults they are usually silent, often being an accidental echocardiographic finding in a subject with tuberous sclerosis complex. In most children, they do not cause any symptom and tend to disappear spontaneously[33,35-39]. Some children have symptomatic blood flow obstruction requiring surgical correction. This is nowadays feasible and the risks are low. There is usually no relapse[32,40]. A few cases may present atrial or ventricular dysrhythmias which commonly regress[33], but which occasionally may be a cause of sudden death[14,41]. The Wolff-Parkinson-White syndrome has also been reported with a greater frequency than in the general population, possibly due to the presence of tumors acting as an abnormal connection at the atrioventricular junction[29,42]. When cardiac rhabdomyomas are detected during prenatal life, the clinical picture is variable and the natural history remains uncertain. Our data concerning the frequent association with arrhythmias, the almost constant association with tuberous sclerosis complex and the tendency towards spontaneous regression are in agreement with those published in the literature. We observed only one fetal demise in a 28-week-old fetus with a giant septal rhabdomyoma causing severe hemodynamic impairment. In the case series published so far, the perinatal mortality, apart from the terminations of pregnancy, was reported to range between 0 and 57% (Table II)[7,21-26]. In accordance with some authors we found that most intrauterine cardiac rhabdomyomas have a benign outcome[21,23]. On the other hand, other authors reported frequent fetal demise and neonatal death[17,18,22,26]. The reasons for this disagreement are unclear: we would like to point out that our cases belong to a low-risk population and that in no case was there a family history of tuberous sclerosis. It is possible that these circumstances could have resulted in a selection bias such that the more serious cases which occur in some referral centers may have been avoided.

However the problem for many, if not all, children with cardiac rhabdomyomas is that the frequent spontaneous regression of cardiac tumors does not mean that they have recovered from the disease. These patients may soon develop cerebral and renal manifestations of tuberous sclerosis complex[2] and have a median life expectancy of 26 years[43].

Tuberous sclerosis complex is an autosomal dominant condition with high penetrance and variable expressivity. It is a multisystem disorder pathologically characterized by the development of hamartomas in multiple organ systems: brain, skin, heart, lungs, and kidneys[44]. Clinical manifestations include epilepsy, mental retardation, skin lesions such as hypomelanotic maculae and facial angiofibroma (adenoma sebaceum),

Table II. Rhabdomyoma during prenatal life: case series.

Author	Cases	Gestation (weeks)	No.	Symptoms	TSC	Outcome
Wallace et al.[21], 1990	4	20-35	3 multiple, 1 single	1 arrhythmia	4	1 operation, 3 alive with total regression
Groves et al.[22], 1992	10	20-34	4 multiple, 6 single	2 arrhythmia, 3 hydrops	2	4 TP, 3 FD, 3 alive with total regression
Holley et al.[23], 1995	17	21-38	9 multiple, 8 single	3 arrhythmia, 2 hydrops	10/17	1 TP, 1 FD, 1 ND, 14 alive (1 operation, 4 no regression, 5 partial regression, 4 total regression)
Sonigo et al.[24], 1996	8	24-35			7/8	5 TP
Beghetti et al.[7], 1997	10			2 arrhythmia		
Gutierrez-Larraya et al.[25], 1997	8	22-38	3 multiple, 5 single	4 arrhythmia, 2 hydrops	1/4	1 TP, 2 ND, 4 alive, 1 lost to follow-up
Geipel et al.[26], 2001	10	22-34	6 multiple, 4 single	2 arrhythmia, 4 hydrops	4/10	3 TP, 1 FD, 2 ND, 4 alive with partial regression
Present series	9	27-36	8 multiple, 1 single	2 arrhythmia, 1 hydrops + arrhythmia	7/9	1 FD, 1 died after operation, 7 alive (6 partial regression, 1 total regression)

With regard to the case series of Sonigo et al. and Beghetti et al., the data are cited for the sake of completeness but it should be noted that they are not sufficient for the present tabulation. FD = fetal demise; ND = neonatal death; TP = termination of pregnancy; TSC = tuberous sclerosis complex.

symptoms resulting from cardiac rhabdomyomas (subaortic stenosis, arrhythmias) and clinical problems secondary to renal lesions. The exact incidence of tuberous sclerosis complex in patients with cardiac rhabdomyomas and, vice versa, of rhabdomyoma in patients with tuberous sclerosis complex is unknown. In patients with cardiac rhabdomyomas, the incidence of tuberous sclerosis has been reported to range between 50 and 90%[28,45,46]. In patients of all ages with tuberous sclerosis complex, the echocardiographic finding of rhabdomyoma has been reported to range between 43 and 72%[29,33,36,47-49] with children having the higher incidence and presenting more numerous and larger tumors[29,50]. In our series of cardiac rhabdomyomas, the incidence of tuberous sclerosis complex was 77%. These figures almost certainly underestimate the real incidence due to the different chronological evolution of the hamartomas in various organs. It is well known that some manifestations of tuberous sclerosis complex such as cardiac rhabdomyomas and renal cysts appear very early during prenatal life or infancy[21,34]. Other manifestations such as adenoma sebaceum and renal angiomyolipomas appear later during childhood or adult life[46]. Cerebral hamartomas may be detected in intrauterine life but manifest clinically later, during the first years of life[24]. Actually cardiac rhabdomyomas are congenital tumors: they arise during the second-third trimesters of fetal life and increase in size and number until the term of gestation[21,22,51]. They have tendency to regress after birth, especially during the first 2-4 years of life or during adolescence[29], although prenatal regression[13,23] as well as postnatal progression in size secondary to corticotropin therapy have occasionally been reported[52]. Therefore, during the first months or years of life cardiac rhabdomyomas may be the only manifestation of tuberous sclerosis complex, whereas in adulthood they are always associated with it. Thus, it is very probable that all fetuses and infants with cardiac rhabdomyomas have tuberous sclerosis. The antenatal detection of fetal cardiac rhabdomyomas should prompt careful examination of the parents and siblings for signs of tuberous sclerosis complex. Most authors recommend detailed skin examination, echocardiography, renal ultrasonography, computed tomography of the brain and fundoscopy. It is also necessary to continue to follow affected children even after tumor regression.

The management of cardiac rhabdomyomas detected during intrauterine life is very difficult because it poses some serious questions regarding the choice of whether to continue or to terminate pregnancy. Whatever the choice, it appears appropriate to support it with clear information about the prognosis. Therefore, it is also important to explain the therapeutic possibilities. The first autopsy series showed a high mortality in infancy. This had prompted some authors to advocate an aggressive surgical approach[53-55]. The usually spontaneous regression and the benign outlook of cardiac rhabdomyomas have been evident since the advent and widespread use of echocardiography[33,35-39,56]. Therefore, an expectant approach is indicated. Surgical treatment should be reserved for those infants with severe blood flow obstruction or intractable life-threatening rhythm disorders[33,37]. However, even if these guidelines are strictly adhered to, in children the rate of operative intervention may still be significant[40]. Furthermore, it is appropriate to remind the readers that current echocardiography cannot exclude very small tumors and the related inherent dangers of arrhythmias and sudden death[29] which probably necessitate a continued cardiologic follow-up.

The outcome of fetal cardiac rhabdomyomas, although dependent on the size and intracardiac location, may be good as far as the course of pregnancy and the evolution of the tumors are concerned, but the prognosis in terms of the development of tuberous sclerosis remains uncertain.

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