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Tuberous sclerosis cases presenting with cardiac mass during the neonatal period

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Summary

The aim of the study is to evaluate the tuberous sclerosis cases diagnosed during the neonatal period presenting with cardiac masses. The clinical and laboratory findings of 4 cases and of tuberous sclerosis diagnosed in Ege University Medical Faculty Newborn Clinic were evaluated retrospectively. The first case was admitted to the Newborn Clinic with the diagnosis of cardiac mass detected at the 28th gestational week. Cranial magnetic resonance imaging revealed subependymal hamartomas. Echocardiography showed large masses within the intraventricular cavity and cardiac apex. The second case was admitted to the Newborn Clinic with the diagnosis of cardiac mass detected at the 29th gestational week. Cranial magnetic resonance imaging revealed subependymal hamartomas and cortical tubers. Echocardiography showed multiple masses located at right ventricular outflow, right atrium and left ventricle. In the third case multiple cardiac masses in both ventricles were detected during the neonatal period. Cranial magnetic resonance imaging showed multiple tubers. The fourth case was admitted to the Newborn Clinic with the diagnosis of cardiac mass detected at the 32th gestational week. Three hypopigmented skin lesions were found. Echocardiography showed multiple masses within the right ventricle, left ventricle and interatrial septum. Cranial magnetic resonance imaging revealed subependymal nodules. Cardiac mass should suggest Tuberous Sclerosis, cranial imaging must be performed. (*Turk Arch Ped 2013; 48: 57-61*)

Key words: Cardiac mass, intrauterine, tuberous sclerosis

Introduction

Primary cardiac tumors are observed rarely in the childhood age group. The most common cardiac tumor in the childhood age group and intrauterine period is rhabdomyoma (RM). RMs in the heart may lead to cardiac failure and hydrops fetalis in the prenatal period and stillbirth. In the neonatal period, it may cause cardiac murmur, cardiac failure and arrhythmia or may be asymptomatic. However, surgical treatment may be performed if it leads to mechanical obstruction or life-threatening arrhythmias. It has been reported that the most common cardiac finding of tuberous sclerosis is rhabdomyomas with a rate of 50-80%. TS should be considered in patients in whom RM is found in the heart because of their common association. In this study, information about intracardiac masses and TS is presented because of four newborn subjects who were found to have intracardiac masses on echocardiographies (ECO) performed three times in the intrauterine period and once in the neonatal

period and diagnosed as tuberous sclerosis with investigations performed in the postnatal period.

Case

Case 1. It was learned that a female patient who was born by cesarean section at the 40-41st gestational week from a 22-year-old G1P0 healthy mother with a birth weight of 3510 g was followed up because of cardiac mass found at the 28th gestational week (Figure 1). Fetal ECHO revealed an appearance of hypertrophy and mass in the interventricular septum and apex. There was no familial history of known disease. On physical examination, no pathology was found except for a 2/6 murmur heard especially in the pulmonic area. Complete blood count and biochemical tests were within normal limits. Electrocardiogram (ECG) revealed sinus rhythm. Echocardiography revealed a large mass in the interventricular septum and apex and normal valve functions. The mass did not

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cause obstruction in the ventricular outlet tract. The patient was investigated in terms of TS considering rhabdomyoma. Cranial and abdominal ultrasonographies were found to be normal. The supratentorial section on cranial magnetic resonance (MR) revealed lesions related to subependymal and periventricular hamartomas in the head of caudate nucleus and around the foramen monro which were hyperdense in the T1-weighted images and hypodense in the T2-weighted images at the level of bilateral centrum semiovale and lateral ventricles with a higher number and larger dimension in the left (Figure 2) and it was reported that these findings supported TS. On ophthalmologic examination, a hypopigmented vegetative lesion was found in the optic disc of the right eye which was considered to be inside the vitreum. Thereupon, orbital computerized tomography (CT) was performed. A noncalcified lesion with a dimension of approximately 2x3 mm was found in the bulbus oculi at the level where the optic nerve enters the bulbus. The appearance was found to be compatible with astrocytic hamartoma when evaluated with brain findings. Electroencephalogram (EEG) revealed no pathology. The patient was monitorized and followed up in terms of arrhythmia. Surgical intervention was not considered, since the mass did not disrupted the hemodynamic balance and the patient was discharged without any problem to come back for follow-up visits.

Case 2. It was learned that a female patient who was born at the 38th gestational week by cesarean section from a 31-year-old G2P1 healthy mother was followed up because of cardiac mass found on ECHO performed at the 29th gestational week. The first child of the family was found to have aortic coarctation and hypoplastic left heart syndrome in the neonatal period and was lost on the fifth day of life because of sudden cardiac arrest. Physical examination was found to be normal. Complete blood count and biochemical tests were found to be normal. Cranial and abdominal ultrasonographies were found to be normal. Electrocardiogram revealed sinus rhythm. On echocardiogram, a mass with dimensions of 8x15 mm in the right ventricular outlet tract, a mass with dimensions of 8x14 mm in the right atrium localized posteriorly which did not compress the inferior and superior vena cava and multiple masses in the left ventricular wall, in the mitral anterior papillary muscle and right ventricular apex with the largest one having a dimension of 8 mm were found. Since the findings were compatible with multiple rhabdomyomas, the case was investigated in terms of TS. The supratentorial sections on cranial MRI revealed diffuse hamartomas in the subependymal white matter which were hyperdense on T1-weighted images and hypodense on T2-weighted images, hamartomas at the level of the foramen monro and suspicious T1 hyperdense lesions which might be related to cortical tubers on T1-weighted images. With these findings the patient was diagnosed as TS. Ophthalmologic examination was found to be normal. Paroxysmal disorder composed of spike waves was found in the occipital regions of the right hemisphere on EEG examination in the patient who had no seizures clinically. Antiepileptic treatment was not started. Surgical

intervention was not considered in the patient, either, since the mass did not disrupt the hemodynamics and did not lead to arrhythmia. The patient who was monitorized and found to have no arrhythmia was discharged to come back for follow-up visits.

Case 3. A female patient who was born at the 37-38th gestational week from a G2P1 healthy mother was started to be followed up because of a cardiac mass found on fetal ECHO. There was no pathology in her personal and familial history. Physical examination revealed no pathology except for a 1/6 systolic murmur heard in the pulmonic area. Complete blood count and biochemical tests were found to be normal. Abdominal and cranial ultrasonographies were found to be normal. Electrocardiogram revealed sinus rhythm. On echocardiogram, a total of three hyperechogenic masses were found in the right and left ventricles near the apex with the one in the left ventricle having a dimension of 12x8 mm and the larger one of the other two ones in the right ventricle having a dimension of 6 mm. Cranial MRI was performed in the patient who was considered to have rhabdomyoma. Nodules typical for tuberous sclerosis were found adjacent to both foramina of Monro. A tuber with a diameter of 5 mm was also found in the left frontal region. With these findings TS was considered and the patient

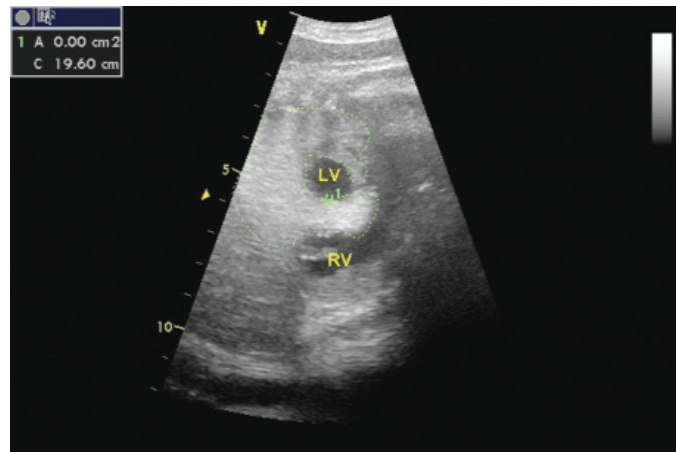


Figure 1. Appearance of the tumor on fetal echocardiogram

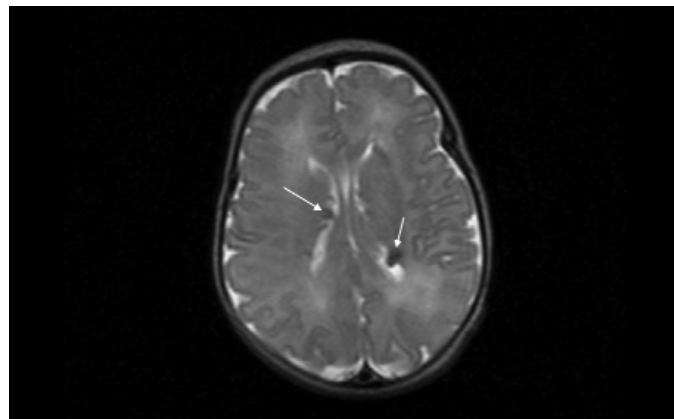


Figure 2. Appearance of hamartomas on magnetic resonance imaging

was monitored. Ophthalmological examination was found to be normal. Electroencephalogram was found to be normal. The patient who had no problem or arrhythmia in the follow-up was discharged to come back for follow-up visits. In the outpatient follow-up visits, it was observed that the cardiac masses disappeared.

Case 4. A male patient who was born at term with a birth weight of 4040 g, referred to our center because of myocardial thickening found on prenatal ultrasonography at the 32-33rd gestational week and found to have an appearance compatible with RM on fetal ECHO performed at the 34th gestational week was started to be followed up. There was no familial history of known disease. Physical examination revealed no pathology except for a 2/6 systolic murmur in the mesocardium and three hypopigmented lesions on the trunk. Complete blood count and biochemical tests were found to be normal. Electrocardiogram revealed sinus rhythm. On postnatal ECHO, three-four masses with the largest one having a diameter of 1.2 cm were found in the right ventricle, five-six masses with the largest one having a diameter of 1 cm were found in the left ventricle and a mass having a diameter of 5 mm was found in the interatrial septum (Figure 3). On abdominal ultrasonography, cystic formations were found in both kidneys and the lesions in the kidneys were evaluated as millimetric simple cysts smaller than 1 cm on abdominal tomography. Cranial MRI revealed subependymal nodules in the bilateral ventricular walls and mass lesion in the parenchyma especially prominent in the left hemisphere. Paroxysmal activity originating from the frontotemporal part of the left hemisphere and temporocentral part of the right hemisphere was observed on EEG in the patient who had no seizures. The patient who had no problem or arrhythmia in the follow-up was discharged to come back for follow-up visits. Antiepileptic treatment was started in the patient who had a seizure at the age of five months and was followed up by the neurology department. Follow-up ECHOs revealed that the cardiac masses were reduced in size.



Figure 3. Appearance of the cardiac masses on ECHO performed at the first hour postnatally.

Discussion

In echocardiography studies, the frequency of primary cardiac tumors in the childhood age group was found to be 0.17% (1). A great majority of primary cardiac tumors are benign. Rhabdomyoma (60%), teratoma (25%) and fibroma (12%) are the primary cardiac tumors which may be observed in the childhood. They develop in the intrauterine period and may be diagnosed early with prenatal ultrasonography. They may lead to fetal arrhythmia, non-immune hydrops fetalis, respiratory distress, cardiac failure and cyanosis or they may be asymptomatic. The rate of asymptomatic rhabdomyoma has been calculated to be 1/326 000 in infants (1). The relation of cardiac rhabdomyomas with TS is well known. It has been reported that cardiac RMs may be one of the earliest signs of TS (2,3). Our patients were diagnosed in the early period by investigations performed because of cardiac mass found in the intrauterine period without a familial history. Cardiac rhabdomyomas are observed with a rate of 60% below the age of two in patients with a diagnosis of TS (4). The frequency of these tumors in the neonatal period is 1/40 000. Cardiac rhabdomyomas in the intrauterine period appear as homogeneous, round and hyperechogenic masses on USG. The ones associated with tuberosclerosis are mostly in the right ventricle and multiple. It was shown that cardiac rhabdomyomas might have dimensions ranging between 4 mm and 55 mm and the tumors enlarged markedly in the second and third trimesters in the intrauterine period (8,10). Both atrial and ventricular masses were found in our second and fourth patients and only ventricular masses were found in our first and third patients. While three of our patients had multiple cardiac masses, our first patient had a large single mass as thickening in the interventricular septum and ventricular walls.

Cardiac rhabdomyomas may be asymptomatic or may be manifested by clinical and hemodynamical findings depending on the number of tumors, localization of the tumor and dimensions of the tumor. In the intrauterine period, they may be found on fetal ultrasonographic screenings or may be manifested as hydrops fetalis. In the postnatal period, they may be completely asymptomatic or they may be manifested by a murmur alone or congestive heart failure, decreased cardiac output due to intracardiac obstructions and arrhythmia and sudden death may occur (1). When the diameter of the tumor mass exceeds 20 mm, the perinatal mortality risk of the fetus is high (10). Arrhythmias, supraventricular and ventricular tachycardia and atrioventricular blocks may generally be observed with rhabdomyomas (6,11). It is thought that the tumor contains embryonic Purkinje cells histopathologically and these constitute an accessory conduction pathway between the atrium and ventricle and cause ventricular preexcitation and arrhythmias (4,12). It has been shown that symptomatic rhabdomyomas have a mortality rate of 53% in the first week (6,13). In our four patients, cardiac complaints and arrhythmia findings on ECG were absent.

In cardiac rhabdomyomas, reduction generally occurs as the age gets older (4). In some studies, they have been shown to regress partially at the age of two and completely at the age of four. In one study, complete regression was found in 28% of the cardiac tumors, partial regression was found in 46% and no change was found in 19% (6,14). In our third patient, the cardiac masses were observed to be disappeared at the age of two.

Treatment is symptomatic. Since reduction occurs most of the time, medical or surgical treatment options are considered depending on the hemodynamics, cardiac pathology and the localization of the tumor. Antiarrhythmic agents may be used in treatment (8). Surgical treatment is recommended in case of mechanical obstruction in the heart or life-threatening arrhythmias. Surgical intervention was not performed in our patients, since they were asymptomatic and their hemodynamic states were not disrupted.

It has been reported that ECHO is important and adequate in the prenatal diagnosis and follow-up of cardiac rhabdomyomas (4,10). Other cardiac tumors which should be considered in the differential diagnosis ultrasonographically include fibroma, mixoma, teratoma and hemangioma. Sonographically, it is not possible to differentiate rhabdomyoma, fibroma and mixoma. Teratomas appear as masses outside the heart and are associated with pericardial effusion. Hemangiomas contain cystic and solid areas and they occur in the right atrium. The diagnosis is made between the 21st and 30th gestational weeks by ultrasonography.

Although fetal ECHO in cases of familial TS is normal at the 18th gestational week, masses may be found in the fetal heart at the 22nd gestational week (15). Since the tumors in the kidneys and brain can not be observed by ultrasonography in these cases, fetal MRI may be performed and the family may be informed about termination of pregnancy within legal limits by explaining neurologic sequelae and the risk of fetal loss (15). An association between cardiac rhabdomyoma and trisomy 21, 13 and 18 has been reported; karyotyping by amniocentesis may be performed after interviewing with the family. Molecular diagnosis can be made in pregnant women with a familial history of TS (16).

Tuberoclerosis is a disease which occurs as a result of spontaneous mutations which inactivate the TSC1 (9q34,3) and TSC2 (16p13,3) genes coding two proteins called tuberin and hamartin (4). It has an autosomal dominant inheritance (5). Its prevalence has been reported to be approximately one in 6 000-12 000 live births. 60-80% of the cases occur with new mutations (6). In rare cases, TSC2 mutation is more frequent. TSC1 and TSC2 mutations have not been found in 20% of the patients with a marked phenotype for tuberoclerosis (7). The disease involves multiple systems. The brain and skin are affected most commonly. The kidney, eye, lung, bone and heart are also affected. Clinically, resistant epilepsy, mental retardation, behavioral problems and skin lesions are observed. Convulsions are the most common reason for presentation and start mostly in the first year of life. In our study, one patient had a seizure at the age of four months and one patient had a seizure at the age

of five months and antiepileptic treatment was started. Genetic studies could not be performed in our patients because of economic problems.

The prominent brain lesion is calcified or non-calcified tuber localized subependimally in the brain hemisphere. Important findings in the diagnosis include subependimal giant-cell astrocytoma and subependimal nodules. Our first patient had hamartomatous lesions and our second, third and fourth patients had subependimal nodules and tubers.

Hypopigmented lesions which are cutaneous findings have an oval or leaf-like shape and different dimensions. They are mostly observed in the trunk and extremities. They become prominent in the first years of life. They may not be observed in the neonatal period, since pigmentation is not developed and may appear in time. Only one of our patients had hypopigmented lesion on the body.

The most common renal lesions in tuberoclerosis include angioliipomas and renal cysts. However, renal carcinomas may also occur. The frequency of renal cysts is not known. One of our patients had bilateral renal cysts.

Patients with tuberoclerosis may have ophthalmological findings including retinal tumors, astrocytic hamartoma, pigment changes in the iris and colobomas. Our first patient had retinal astrocytic hamartomas.

It should be kept in mind that cardiac rhabdomyoma in the neonatal period may be associated with TS even though other clinical findings of TS are absent and diagnostic laboratory tests should be performed.

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