Prenatal diagnosis of tuberous sclerosis through the detection of cardiac rhabdomyomas: a review from the literature


1 Department of Clinical and Experimental Medicine and Pharmacology, University of Messina, Italy
2 Department of Gynecological, Obstetrical Sciences and Reproductive Medicine, University of Messina, Italy
3 Unit of Genetics and Paediatric Immunology, Department of Pediatrics, University of Messina, Messina, Italy
4 Unit of Vascular Surgery, University of Messina, Italy
5 Department of Radiology Sciences, University of Messina, Italy
6 Department of Neurosciences, Psychiatric and Anesthesiological Sciences, University of Messina, Italy
7 Department of Formative Processes, University of Catania, Catania, Italy

Abstract

Tuberous sclerosis complex (TSC) is an autosomic dominant genetic disease frequently due to the mutation of the oncosuppressors genes TSC1 and TSC2. TSC results in different phenotypical and clinical aspects consisting in hamartomatous lesions, primarily involving the skin and the central nervous system and multiple rhabdomyomas, involving mainly heart chambers. The detection of multiple cardiac rhabdomyomas in prenatal age, through fetal ultrasonography performed at several gestation weeks, is often the only one manifestation of the TSC, providing to an early diagnosis for better comprehensive care for affected individuals.

Introduction

Cardiac Rhabdomyoma (CR) is the most common primary cardiac tumor in infancy with an estimated incidence of 0.08 percent. It is a benign hamartoma arising from embryonic myocytes. An early diagnosis of cardiac rhabdomyoma can be crucial to make an early diagnosis of tuberous sclerosis complex (TSC), in fact in 80 percent of cases, CR is associated with tuberous sclerosis; conversely, 60 percent of children with TS have documented CRs. Tuberous sclerosis is a genetic disease with tumors developing in the brain, kidneys, heart, eyes, lungs, and skin. It can be more difficult to manage the disease if it is discovered too late, and an early discovery of disease can be useful to help the parents to know it and to do the best choice for the child future life. A meta-analytical approach to the prenatal management of rhabdomyoma associated with tuberous sclerosis (TS) is lacking.

We tried to collect all cases of tuberous sclerosis with CR of the last 14 years to have an easier diagnosis of TS.

Methods

Our purpose was to highlight the importance of the connection between the detection of cardiac rhabdomyomas in gestational age and an early diagnosis of tuberous sclerosis, in relation to characteristics of the patients taken into exam. Particularly, cases were searched on Pubmed by entering the strings: "prenatal cardiac rhabdomyoma and tuberous sclerosis." Thus, we retrieved a total of 20 cases That Were Observed in 14 years 1994 to 2011 (Table 1). We excluded some articles that hadn't information useful for the research, therefore 20 is the number that we considered for the research. Of the 20 Patients, we know gestational age of 19 mothers, maternal age of 16 mothers, familiar history of 17 mothers. 8 mothers had at that moment other diseases that we considered to get information about comorbity. 19 mothers were subjected to fetal ultrasonography, 18 had cardiac rhabdomyomas, 14 mothers had tumors in other locations and the heart wasn't the only organ affected.

Results

A summary of the patient history, clinical and echocardiographic findings are reported in Table 1.

From a total of twenty cases, in fourteen cases the findings were multiple cardiac Rhabdomyomas and in six cases the ultrasounds showed single cardiac rhabdomyomas. The diameter of the mass was reported in fiftheen cases, in five cases no data about the mass diameter is available. The mean diameter of the masses were 41 mm (range 8 – 41 mm). In seven patients the tumor location was detected in left and right ventricle, in five patients tumor was confined only to the right ventricle, in one patient tumors were found in both ventricles, in one patient only the right ventricle, and in five patients the tumor location was not reported. Extracardiac lesions were reported in four patients consisting in skin depigmentation in two patients (detected
Tuberous sclerosis was genetical confirmed in eleven patients, in eight patients the diagnosis was negative and in one patient there was no reported diagnosis. In three cases with positive familiar history, tuberous sclerosis complex in the young patients was confirmed by genetic diagnosis, in one case with positive familiar history no data was reported. In three cases with coexist extracardiac lesions, the diagnosis of tuberous complex was confirmed by genetic tests, in one case there was no data reported. In the six patients with cardiac heart defects associated, in three cases the diagnosis of TSC was confirmed by genetic tests, in one case there was no data reported.

Fig.1 CR involving interventricular septum  
Fig.2 CR involving left ventricle

Discussion
Cardiac rhabdomyomas are the most common cardiac tumors, accounting for the 60-80% of primary cardiac tumors. Other cardiac tumors include fibroma, myxoma, teratoma and hemangioma. Prenatally findings can be detected by routine ultrasound scanning of the fetus, performed with traditional ultrasonographic projection views at different gestational weeks. Cardiac rhabdomyomas are localized mainly in the ventricles but they also can be detected in the aorta. In the majority of patients this lesions are asymptomatic, but when the location is intracavitary or the tumor is characterized by a big volume, it can determine outflow or inflow obstruction or congestive heart failure. In several cases the intramural location can determine different arrhythmias, including supraventricular tachycardia and Wolff-Parkinson-White syndrome. Histologically, this benign lesions are composed of large and irregular cardiac myocytes with centrally placed glycogen-filled cytoplasm and fluid. The radiating strands of cytoplasm that stretch from the central nucleus to the cell membrane give the cells a “chickenwire” appearance. Ultrasonographically, cardiac rhabdomyomas appear like homogenous and hyperechogenic masses localized in different locations, but mainly to the ventricles and septal wall. Especially when multiple, they are frequently associated with tuberous sclerosis complex (TSC), and the ultrasonographic findings of cardiac rhabdomyomas are one of the major feature for the diagnosis of TSC.

Tuberous sclerosis in an autosome dominant genetic disease with variable penetrance, the incidence is about 1/30,000 in newborn children. The genetic basis of tuberous sclerosis is heterogeneous, it may be caused by the mutation of the tumor suppressor genes TSC1 or TSC2. Diagnostic criteria for tuberous sclerosis complex were revised by a consortium in 1998, and recommendations for the diagnostic evaluation were proposed on 1999. In this artile we collected a total of twenty case found in literature from 1998 to 2011. In fourteen cases in which multiple cardiac rhabdomyoma are detected, the 71.42% is associated to TSC diagnosis confirmed by genetic tests. No diagnosis were made in patient with single cardiac rhabdomyoma. The total incidence of TSC in the patients described was of 55.00%.

Cardiac rhabdomyoma may be the earliest sign of TSC in uterus and can precede the detection of brain and kidney lesions. The detection of cardiac tumors can be use as a warning sign for TSC and may require genetic counseling. Despite the limits of the search, our purpose is to show that prenatal detection of cardiac rhabdomyomas, in particular when multiple tumors are found in ventricles and family history is positive, there’s a strict association with TSC, and fetal echocardiography is useful in the detection of the lesions, showing itself as a powerful tool for an early diagnosis of tuberous sclerosis complex.

References