Tuberous Sclerosis Complex in Children with Apical Hypertrophic Cardiomyopathy as the First Manifestation: A Case Report and Literature Review

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Case report

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Abstract

**Background:** Tuberous sclerosis complex (TSC) is a rare autosomal dominant hereditary neurodermal syndrome with diverse clinical manifestations, implicating multiple organs including the nervous system, skin, kidney, lung, heart, eyes and others. Most of the children are first diagnosed with seizures or facial hemangiofibroma, 45% to 60% of patients with TSC lesions can affect the heart resulting in cardiac rhabdomyoma. Although most cardiac rhabdomyomas are asymptomatic, some children may develop severe symptoms such as hemodynamic abnormalities, arrhythmias, and even heart failure in the neonatal period and early infancy. But Tuberous sclerosis complex with apical hypertrophic cardiomyopathy as the first manifestation is rare. Hence, physicians may delay diagnosis and treatment of TSC due to the lack of comprehensive thinking on this atypical presentation.

**Case presentation** A 5-year-old girl was admitted to our hospital due to syncope for more than 10 days. When she was 8 months old, she was diagnosed with hypertrophic cardiomyopathy and received long-term oral propranolol treatment. After her admission, a thorough examination was performed. Heart exam revealed the revelant problem. Brain MRI demonstrated mutiple nodules in bilateral frontal parietal occipital cortex, subcortical cortex and bilateral lateral ventricular margin consistent with TSC. Genetic analysis (high-precision clinical display PLUS, JiaJian Medicine Company) revealed that the patient had inherited the TSC2 mutation c.1343T> C (p.L448P) from her mother (heterozygous), who was clinically unaffected.

**Conclusions:** This report highlights that TSC occurs in different ways. Given the possibility of insidious and atypical tuberous sclerosis, when apical hypertrophy or cardiac tumors are identified, it is recommended to broaden the systemic examination even including genetic testing to further determine the cause, in order to reduce the misdiagnosis rate of tuberous sclerosis.

**Background**

Tuberous sclerosis complex (TSC) is an autosomal dominant hereditary skin neurological syndrome. It was first described by Recklinghausen in 1862. Its estimated incidence and prevalence are one in 6000 to 10,000 live births and one in 20,000 persons, respectively[1]. The clinical manifestations of this disease are complex and diverse, most commonly with skin lesions, nodules in the brain, cardiac rhabdomyomas, pulmonary angiolymphomas, renal leiomyomas, hamartoma lesions in other organs and neuropsychiatric symptoms. It was not until the 1980s that TSC was first diagnosed based on severe and typical clinical manifestations.

Current research has found that TSC1 and TSC2 are the pathogenic genes. Among them, the TSC2 mutation rate is about 70%, while the TSC1 mutation rate is about 20%, and about 10–20% of TSC children have no recognized genetic mutations, suggesting that other pathogenic genes may be present in addition to TSC1 and TSC2[2, 3]. Most children with TSC are first diagnosed with seizures or facial hemangiofibroma. 45–60% of patients with TSC manifest heart dysfunction and develop
rhabdomyosarcoma. More than 90% of cardiac tumors found during the fetal period and within one year after birth are cardiac rhabdomyomas. Prenatal ultrasound examination of fetal cardiac rhabdomyosarcoma is an early clue to the diagnosis of TSC[4]. Although most cardiac rhabdomyomas are asymptomatic, some children may develop severe symptoms such as hemodynamic abnormalities, arrhythmias, and even heart failure in the neonatal period and early infancy. This article presents a case of childhood tuberous sclerosis complex with apical hypertrophic cardiomyopathy as the first manifestation in clinical work, and reviews relevant literature, exploring the clinical manifestations and characteristics of heart damage in TSC

**Case Presentation**

A five-year-old female child was admitted to the Children's Cardiovascular Specialty of our hospital for "intermittent syncope for more than 10 days" in September 2019. The child had recurrent syncope for 10 days, all of which were sudden onset, without convulsions, manifested as refractory, with cyanosis of the lips, resolved spontaneously within 1 to 2 minutes, with no chest tightness, palpitation or other discomforts. The outpatient was admitted to hospital for "syncope pending investigation"

Tracing the patient's history, we found that the child was admitted to our hospital for recurrent respiratory infections at the age of 8 months. At that time the color Doppler ultrasound showed that the left ventricle had a thickened apex (8mm), the ventricular septum was thickened (5mm), and the left ventricular posterior wall was thickened (6mm). The papillary muscles were also significantly thickened. At that time, she was diagnosed with hypertrophic cardiomyopathy, and received long-term oral propranolol treatment. She also had a history of febrile seizures at the age of 2 years, but had not undergone brain imaging testing. There was no similar medical history in the family.

After admission, physical examination revealed arrhythmia without obvious pathological murmur. Vital signs were stable with a pulse of 80 beats per minute, a respiratory rate of 22 beats per minute, body temperature at 36.9°C and consciousness. Neuropathological signs were negative. Other examinations (face, lips, skin) were unremarkable. After admission, additional examinations were completed, including routine blood analysis, liver and kidney function, electrolytes, blood glucose, myocardial enzyme spectrum, BNP, and etiology examination. No obvious abnormalities were found. ECG showed sinus arrhythmia, myocardial damage and delay of intraventricular conduction (Figure 1). Results of echocardiography indicated that the left ventricular apex was round and blunt, partially bulging outward, with a range of 12×10mm. (Figure 2). Chest CT revealed that the local apex of the left ventricle was slightly raised with low-density shadows in the anterior region of the heart (Figure 3). EEG manifested as abnormal with slightly sharper waves in the left anterior temporal region. Brain MRI demonstrated multiple nodules in the bilateral frontal parietal occipital cortex, subcortical cortex and bilateral lateral ventricular margin consistent with TSC (Figure 4). Based on this, the patient was clinically diagnosed as TSC. Genetic analysis (high-precision clinical display PLUS, JiaJian Medicine Company) revealed that the patient had inherited the TSC2 mutation c.1343T> C (p.L448P) from her mother, who was heterozygous and clinically unaffected. Therefore, the patient's terminal diagnosis was TSC.
**Discussion And Conclusion**

**1. Briefly description of TSC and its characteristics**

Tuberous sclerosis complex is an autosomal dominant hereditary disease. Clinically, it is characterized by cutaneous sebaceous adenoma, epilepsy, and mental retardation. It can also affect multiple systems such as the kidney, heart, lungs, and eyes, manifesting as multiple hamartomas throughout the body[5, 6]. Tuberous sclerosis is primarily caused by mutations in the TSC1 or TSC2 genes. The TSC1 gene encodes the hamartin protein and the TSC2 gene encodes the tuberin protein. These two proteins form a complex that inhibits the mTOR pathway, regulates cell growth and metabolism, and inhibits abnormal cell proliferation, tumor cell formation and metastasis[7-9]. When the TSC1 or TSC2 gene is mutated, activation of the mTOR pathway leads to abnormal cell proliferation, causing tumor-like lesions[10].

Until the 1980s, scholars diagnosed TSC based on severe and typical clinical manifestations. In 1992, the International Tuberous Sclerosis Association (NTSA) formulated the diagnostic criteria for tuberous sclerosis[11]. In 1998, the diagnostic criteria for TSC were based on the clinical and mutational characteristics of tuberous sclerosis[12]. Revisited in 2012, the International Tuberous Sclerosis Alliance further improved this standard, adding genetic testing to the diagnostic criteria[1].

Detection of pathogenic TSC1 or TSC2 gene mutations in genetic diagnosis can be used as a separate diagnostic criterion. Clinical diagnostic criteria include 11 major diagnoses and 6 minor diagnoses; the main criteria include H hypomelanotic macules (≥3, at least 5mm diameter), A Angiofibromas (≥3) fibrous cephalic plaque, U Ungual fibromas(≥2), S Shagreen patch, M Multiple retinal hamartoma, C Cerebral cortical dysplasia, N Subependymal nodules, G Subependymal giant cell astrocytoma, R Cardiac rhabdomyoma, P Pulmonary lymphangioleiomyoma and angiomyolipomas(≥2). Minor criteria include: C “Confetti” skin lesions, D Dental enamel pits (≥3), F Intraoral fibroma (≥2), A Retinal achromic patch, M multiple renal cysts, and N non-renal hamartoma. The disease can also be diagnosed when two major criteria or one major criterion and two minor criteria are met[1].

**2. The diagnosis and treatment process in this case**

In this case, the onset occurred in infancy, with cardiac damage as the first symptom, and cardiac color Doppler ultrasound mainly manifested as apical hypertrophic cardiomyopathy. During the follow-up process, no clinical manifestation of other systems has appeared, and the diagnosis was "hypertrophic cardiomyopathy", which had been treated with beta-blockers orally. More than 10 days before admission, paroxysmal syncope appeared. Because of her "heart disease history", she was admitted to the hospital and the possibility of "cardiogenic syncope" was first considered. The electrocardiogram on admission showed sinus arrhythmia, myocardial damage and delay of intraventricular conduction. In order to further clarify the diagnosis and eliminate syncope caused by intermittent arrhythmia, dynamic electrocardiogram was performed in this patient. The result showed that atrial premature beats, some of which were triad, with occasional ventricular premature beats and delay of intraventricular conduction...
myocardial damage and abnormal Q wave. Color Doppler ultrasound indicated obtuse left ventricular apex, local ventricular aneurysm formation, abnormal motion of the segmental ventricular wall and papillary muscle echo enhancement. Cardiac biomarkers were almost normal including AST (26U/L), CK (152U/L), LDH (279U/L), and cTnI<1.9pg/mL. However NT-proBNP was increased 401.9pg/mL. Although cardiac syncope was highly suspected, epilepsy needed to be further excluded given the history of febrile convulsion. Thus EEG and brain MRI were required to further clarify the diagnosis. On the second day of admission, during rounds, "syncope" occurred suddenly, manifested as head tilting to one side, unresponsiveness without twitches and soft bilateral limbs. The seizure lasted for approximately 30 seconds and then resolved spontaneously without incontinence. Checking her medical history with her parents confirmed that similar seizures had occurred in the past and were called "syncope". Therefore, clinical considerations were corrected to "epilepsy" rather than "syncope". Subsequent examination results were reported successively: an abnormal children's EEG was reported, with slightly more sharp waves in the left anterior temporal region. Brain MRI diagnosis indicated bilateral frontal parietal occipital cortex and subcortical abnormal signal focus, with bilateral lateral ventricle marginal nodules considered to be caused by tuberous sclerosis (TS), which is consistent with the diagnosis of tuberous sclerosis. Further genetic testing detected the TSC2 gene mutation, which is consistent with the diagnosis of tuberous sclerosis.

3. Inspiration from the diagnosis and treatment of this case

In this case, a child with a recurrent respiratory infection at the age of 8 months underwent a color Doppler ultrasound examination, which was identified as "apical hypertrophic cardiomyopathy", without related clinical manifestations, so she was allowed to follow up in the clinic regularly. Apical hypertrophic cardiomyopathy is a special type of primary hypertrophic cardiomyopathy, which was first discovered and proposed by Yamaguchi et al in 1976[13]. Apical hypertrophic cardiomyopathy is characterized by bellowing the level of the left ventricular papillary muscle, and is generally not accompanied by left ventricular outflow tract stenosis and pressure gradient, which have little effect on cardiac hemodynamics[14]. Its clinical symptoms are not obvious, and the onset is unknown. The incidence of apical hypertrophic cardiomyopathy varies in different populations in different countries. The incidence of the disease in Japan is 15%, which is about five times that of the United States, while the incidence in Asians can be as high as 40%[15, 16]. The disease is usually more common in middle-aged men, but due to the atypical clinical symptoms of the disease, the age of diagnosis is generally later than the age of onset[17]. The clinical manifestations of the disease are atypical. Only some patients present with atypical chest pain, low exercise tolerance, syncope, etc., so they are easily misdiagnosed and missed. They are often accidentally found when performing cardiac ultrasound or electrocardiogram[18]. Apical hypertrophic cardiomyopathy is mainly diagnosed through electrocardiographic specific changes combined with cardiac color Doppler ultrasound or cardiac magnetic resonance. The electrocardiogram shows a characteristic huge negative T wave, and the color Doppler ultrasound shows a left ventricular apical and end-diastolic apical wall thickness $\geq 15\text{mm}$, and the ratio of the maximum apical wall thickness to the left ventricular posterior wall thickness $\geq 1.3$[19]. Cardiac magnetic resonance(CMR) can
determine myocardial hypertrophy segments more clearly than cardiac color Doppler ultrasound; accordingly it is the gold standard for the diagnosis of apical hypertrophic cardiomyopathy. AHCM is mainly manifested as thickened apical ventricular wall in CMR, which is spades-like[20].

In the present case, TSC was missed in the early stage due to the absence of skin, nervous system and other involved systems, and the color Doppler ultrasound showed "apical hypertrophic cardiomyopathy" rather than "cardiac rhabdomyosarcoma". The diagnosis of TSC was not made until the patient presented with additional symptoms and was confirmed with the MRI results combined with medical history. 45% to 60% of patients with TSC present with heart symptoms and develop rhabdomyosarcoma. Cardiac rhabdomyomas (CR) are mostly found in the fetal or infant period. On the echocardiography of the heart, abnormal areas of enhanced echo in the myocardium often appear in the ventricle, ventricular septum and papillary muscle[21], but appearance in the apical area is rare. The severity depends on tumor size, location, and number, etc [22].

Therefore, identification of unusual manifestations of enhanced echo in the myocardium by cardiac color Doppler ultrasound should lead to a consideration of the possibility of cardiac tumors. The emergence of many cardiac tumors may suggest a certain genetic disease syndrome. Among them, rhabdomyosarcoma is the most common benign cardiac tumor in children. It can be the first clinical manifestation of tuberous sclerosis and an important clue in the diagnosis of tuberous sclerosis [23].

4. Conclusion

Although cardiac rhabdomyosarcoma is typically identified in the ventricle and ventricular septum, it may still be located in the apex, which is a point that is easily confused with apical hypertrophic cardiomyopathy. Both have been ascribed to genetic mutations. However, apical hypertrophic cardiomyopathy has its unique ECG manifestations, and lesions are mainly located in the heart, and do not involve the whole body system, in contrast to cardiac rhabdomyomas, which highlights a major difference between the two diseases. Given the possibility of insidious and atypical tuberous sclerosis, when apical hypertrophy or cardiac tumors are identified, it is recommended to broaden the systemic examination even including genetic testing to further determine the cause, in order to reduce the misdiagnosis rate of tuberous sclerosis.

Abbreviations

TSC: Tuberous sclerosis complex

MRI: Magnetic resonance imaging

ECG: Electrocardiograph

CT: Computer tomography
EEG: Electroencephalogram
AST: Aspartate transaminase
CK: Creatine kinase
LDH: Lactate dehydrogenase
cTnI: Cardiac troponin I
NT-proBNP: N-termina pro brain natriuretic peptide
TS: Tuberous sclerosis
CMR: Cardiac magnetic resonance
AHCM: Apical hypertrophic cardiomyopathy
CR: Cardiac rhabdomyoma

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Author Contributions

YXL H, HL L participated in conception and design. YXL H, T H, Y W, XF H, HL L participated in data acquisition and analysis. YXL H, HL L participated in the writing and revising of the article. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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Figures

Figure 1

Electrocardiogram showed sinus arrhythmia, myocardial damage and delay of intraventricular conduction.

Figure 2

Echocardiography showed that the apex of the left ventricle was round and blunt, partially bulging outward, with a range of about 12×10mm.
Figure 3

Chest CT revealed that the local apex of the left ventricle is slightly raised and low-density shadows were present in the anterior region of the heart.

Figure 4

Brain MRI showed multiple nodules in bilateral frontal parietal occipital cortex, subcortical cortex and bilateral lateral ventricular margin.

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