Case Report

Tuberous sclerosis with cardiac rhabdomyoma: a case report

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ABSTRACT

Tuberous sclerosis or tuberous sclerosis complex (TSC) is a genetic disorder, caused by mutations on either of two genes TSC1 and TSC2. Clinical manifestations are caused by growth of benign tumours in different parts of the body. Ten months old female child with four major criteria of tuberous sclerosis complex and asymptomatic cardiac rhabdomyoma is presented. A case of TSC warrants cardiac evaluation for the presence of cardiac rhabdomyoma and if a cardiac rhabdomyoma is detected on antenatal ultrasound or postnatal echocardiography, one should have high index of suspicion for the diagnosis of TSC. Continued research on this disease has unfolded many realities regarding its etiology as well as treatment.

Keywords: Infantile spasms, Neuro-cutaneous, Rhabdomyoma

INTRODUCTION

Tuberous Sclerosis is a genetic disorder caused by mutations on either of two genes, TSC1 and TSC2, which encode for the protein hamartin and tuberin respectively. These proteins act as tumour growth suppressors that regulate cell proliferation and differentiation.¹ Prevalence is estimated to be 1 in 6000 newborns. It is characterized by growth of benign tumors in brain, heart, lungs, eyes, kidneys, skin and other organs leading to seizures, intellectual disability, autism or developmental delay. Tuberous sclerosis has no cure, but treatment in the form of drugs, educational and occupational therapy can help relieve symptoms.

CASE REPORT

An eleven months old girl presented with repeated episodes of afebrile generalised tonic clonic seizures associated with loss of consciousness for last nine months. Antenatal, natal and postnatal history was insignificant. Developmental milestones were normal. On examination, child was active and playful. Weight, length

and head circumference were appropriate for age. Skull shape was normal. Hypopigmented macular skin lesions (Ash leaf macules) of varying size and shapes were noticed since birth with subsequent increase in number of lesions. A total of seven Ash leaf macules were noted over right popliteal fossa, flexor aspect of right and left leg, middle of forehead and left index finger varying in size from the smallest measuring 0.6 x 0.5 cm to largest measuring 4 x 1 cm. (Figure 1). Tuft of hypopigmented hair was present on scalp anteriorly. Oral cavity was normal. Tone, power, muscle bulk, deep tendon reflexes were normal in all the extremities. No skeletal deformity was observed. Systemic and ophthalmological examinations were normal. MRI Brain showed bilateral subependymal nodules and cortical tubers (Figure 2). Ultrasound abdomen did not reveal any abnormality in the kidneys. Electrocardiogram and Chest X-ray were normal. 2-D and Doppler echocardiography showed a non-obstructing mass in right ventricle of 1.2 cm diameter attached to right ventricle free wall (Figure 3). No mass was noted in left ventricle cavity. Biventricular systolic functions were normal. Child was started on antiepileptic medication and was kept on cardiology and

neuroradiology follow up to track the evolution of disease process.

Figure 1: Ash leaf macules and tuft of hypo pigmented hair.

Figure 2: MRI brain showing sub endependymal nodules and cortical tubers.

Figure 3: ECHO showing right ventricle cardiac rhabdomyoma.

DISCUSSION

Tuberous sclerosis complex (TSC) is a rare multi-system genetic disease characterized by non-malignant tumors in the brain and other vital organs such as the kidneys, heart, eyes, lungs, and skin.¹ Mutation of either of two genes, TSC1 and TSC2, which encode for the proteins hamartin and tuberlin respectively are responsible for Tuberous sclerosis complex.² TSC1 is located on chromosome

9q34 and TSC2 is located on chromosome 16p13. These proteins inhibit the activation of mTOR (mammalian target of rapamycin) which is master regulator of cell growth. Loss of regulation of mTOR in cells lacking either hamartin or tuberlin, leads to abnormal differentiation and development. Two thirds of TSC cases result from sporadic genetic mutations, which can be transmitted to their offspring. TSC1 and TSC2 genes function according to Knudson's "two hit" hypothesis meaning thereby that second random mutation must occur before a tumour can develop which explains its wide expressivity in spite of 100% penetrance. Genetic diagnostic criteria include identification of either TSC1 or TSC2 gene mutation.³

Definite diagnosis requires presence of least 2 major or one major plus 2 minor features. Possible diagnosis is made when 1 major or >2 minor features are present.³

Major features include

- Hypomelanotic macules (≥ 3 , at least 5 mm diameter)
- Angiofibromas (≥ 3) or fibrous cephalic plaque
- Ungual fibroma (≥ 2)
- Shagreen patch
- Multiple retinal hamartomas
- Cardiac rhabdomyoma
- Cortical dysplasia
- Subependymal nodules
- Subependymal giant cell astrocytoma
- Angiomyolipoma (≥ 2)
- Lymphangioleiomyomatosis.

Minor features include

- Multiple dental pits (>3)
- Intraoral fibromas
- Retinal achromatic patch
- Confetti skin lesions
- Nonrenal hamartoma
- Multiple renal cysts.

Involvement of central nervous system in the form of sub-ependymal nodules, cortical/subcortical tubers and sub-ependymal giant cell astrocytoma is the classical feature of TSC. The neurological manifestations include epilepsy, cognitive impairment, autism spectrum disorders, broader pervasive development disorders and infantile spasms. Approximately 50% of people with TSC exhibit cardiac rhabdomyoma, a benign tumour of cardiac muscle on echocardiography. Number can vary and may tend to be located at apex of left ventricle. Majority are asymptomatic but congestive heart failure, arrhythmias and cardiac murmur may be detected in some of the cases. Spontaneous resolution may occur in first year of life although the exact mechanism is not yet well understood. Partial regression of the cardiac rhabdomyoma was reported in 50% of cases and complete resolution in 18% in a series of 154 patients

with tuberous sclerosis.⁴ Cardiac rhabdomyomas are usually not operated upon unless they are obstructive, cause heart failure or are complicated with severe intractable arrhythmias.⁵ Due to their location deep in myocardium complete removal is difficult. No embolic events have been reported and there is no need for oral anticoagulation in the absence of a specific indication (for example, atrial fibrillation). Annual or biannual echocardiograms to detect haemodynamic compromise and annual Holter monitoring to detect severe arrhythmias are recommended. Symptoms are related to the size of the tumours and their location. Complications occur almost exclusively during pregnancy or within the child's first year. Antenatal detection is possible as early as 20 weeks' gestation.⁶ Some patients stabilize after medical treatment with digoxin and diuretics and eventually improve while others require surgery.⁷

Dermatological abnormalities include hypomelanotic patches (ash leaf macules), facial angiofibromas also known as adenoma sebaceum presenting as reddish spots on nose and cheeks in butterfly distribution. Periungual fibromas also known as Koenen's tumors are small fleshy tumors which grow around and under the toenails or fingernails. Shagreen patches are thick leathery pigmented areas present on lower back or nape of the neck. Ophthalmological lesions include retinal or astrocytic hamartomas and non-retinal lesions like coloboma, angiofibroma of eyelids and papilledema. Everolimus is effective in treating refractory seizures and reducing the volume of renal angiomyolipomas and lymphangiomyomatosis as well as facial angiofibromas. Oral rapamycin has been shown to cause regression of astrocytomas associated with TSC and can be a promising alternative to operative therapy.⁸ Everolimus and rapamycin act by inhibiting mTOR, thus blocking the effect of loss of function of TSC1/TSC2. Disease progression is very slow and prognosis is highly variable. Those with mild symptoms can have normal life expectancy. Brain tumours, kidney lesion or lymphangiomyomatosis can be life threatening. With appropriate medical care, most individuals with this disorder can look forward to normal life expectancy. MRI brain and renal imaging needs to be done every 1- 3 year during follow up.

The index case presented with four major criteria in the form of subependymal nodules, cortical tubers, ash leaf macules, and asymptomatic cardiac tumour without any family history. Child was put on antiepileptic medication and was kept on cardiology follow up to monitor evolution of cardiac tumour. The possibility of TSC

should be kept in mind when assessing a child with seizures particularly infantile spasms. There is need to generate awareness regarding extremely heterogenous nature of disease with wide clinical spectrum, need for continued surveillance regarding disease progression, emerging therapeutic options in the form of mTOR inhibitors, ongoing research regarding methods of prevention and ultimately cure for their disorder.

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