A Case Report of Tuberous Sclerosis in Two Generations

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Abstract

Tuberous sclerosis complex [TSC] is a genetic multisystem disorder characterised by the growth of numerous hamartomas in several organs including the brain, heart, skin, eyes, kidney, lung and liver. The affected genes are TSC1 and TSC2 encoding hamartin and tuberin respectively. TSC has a wide range of severity and some people with this condition will only be mildly affected. At present it is impossible to accurately predict who will remain only mildly affected and who will be more severely affected by TSC. Even members of the same family can be affected differently. Many family members show signs of being carriers of the genes for the disease when carefully examined. This article reports a family with documented Tuberous sclerosis in two generations involving three members which is a rare entity.

Introduction

Tuberous sclerosis complex is a genetic disorder of hamartoma formation in many organs particularly the skin, brain, eye, kidney and heart. The characteristic skin lesions are angiofibromas, shagreen patches, periungual fibromas and ash leaf white macules classically although not invariably seen in association with epilepsy and mental retardation. It is caused by mutations on either of two genes TSC1 and TSC2 which encode for the proteins hamartin and tuberin respectively. These proteins act as tumour growth suppressors that regulate all proliferation and differentiation.

The disorder affects about one in ten thousand persons in the general population and has an estimated incidence of one case per 6,000 live births. Thus, it is the second most common neurocutaneous syndrome after neurofibromatosis. TSC has no predilection for gender or race. Affected members of the same family may be of normal intelligence, or they may be severely mentally retarded with seizures that are difficult to control. Cutaneous findings are usually the first clue that patient has TSC but other features may lead to diagnosis. TSC occurs in all races and ethnic groups and both genders. Definite TSC is diagnosed when either 2 major features (out of total 11) or one major feature with 2 minor features (out of total 9) are present. TSC has no cure but treatment as medicines, educational and occupational therapy can help to relieve symptoms.

Mildly affected carriers of the gene are difficult to detect. We report documented familial TSC in two generations of one family.

Case Report

A 28 yr old male patient was brought to our hospital with the complaints of fever, cough and convulsions for the last three days. First day he had two attacks lasting for 2 minutes without loss of consciousness. Second day he had 5-6 attacks lasting for 5 min followed by loss of consciousness for 5-10 min. Third day he had one attack lasting for 5 minutes followed by loss of consciousness for 5 hours. The convulsions were generalised tonic clonic type and were associated with urinary incontinence, frothing from mouth and up rolling of eye balls. He had no tongue bite. He had past history of convulsions since the age of 5 yrs and...
had been on antiepileptic medications but convulsions were not under control. He used to get 2-3 attacks/month without loss of consciousness and there was no h/o post ictal confusion.

The fever was intermittent, moderate grade not associated with chills and rigors. Cough was insidious onset and productive. There was no h/o chest pain or breathlessness. He was treated with bolus doses of inj. Phenytoin and antibiotics which controlled the seizures.

On examination he was found to be semiconscious and restless. He was febrile. Physical signs included angiofibromas over the face and no other skin lesions were present (Figure 1). He was slightly pale. Investigations showed Hb 12.0 gm/dl, WBC-13,600/cumm, Platelets 3,28,000/cumm, ESR-60 mm/hr. Routine urine examination was normal. CT scan brain showed multiple small calcified tubers in bilateral cerebellar hemisphere, left temporal lobe, caudate nucleus and bilateral parietal periventricular region (Figure 2). USG and CT scanning of abdomen showed angiomyolipoma in right kidney and left kidney was normal (Figure 3). Chest X-ray showed right perihilar patchy pneumonitis. 2-D Echo was normal.

Fundoscopy was normal. He had an electrolyte imbalance (Na + 132.7 mm/dl K + 3.2 mm/dl).

Patient has three brothers and two sisters, who are unmarried (Figure 4). There is a family history of skin lesions over the face of his mother and younger brother since their childhood. His mother had two attacks of convulsions at her younger age, after that she did not develop any further attacks. No other family members had h/o convulsions. Other family members did not have any skin lesions. O/E both mother and brother had angiofibromas over the face (Figure 5). Now brother has started developing same lesions over the neck and chest. Wood’s lamp examination did not reveal any ash leaf spots. Other family members did not have angiofibromas or any other skin lesions. Blood reports of all the family members were normal. His younger brother’s CT scan brain revealed multiple 2-17 mm calcified tubers in bilateral cerebellar hemisphere and bilateral periventricular white matter in cerebral hemisphere. Mild peri lesional white matter oedema in the left cerebellar hemisphere (Figure 6). His mother’s MRI scan of brain was normal but USG and CT scanning of abdomen showed angiomyolipoma in both kidneys (Figure 7). 2D Echo of both the mother, younger brother and other family members were normal. CT scanning of brain and abdomen of other family members were normal. All the family members have normal intelligence. Fundoscopy of all the family members was normal. All his siblings were unmarried.

**Discussion**

Tuberous sclerosis complex [TSC] is an autosomal dominant disorder that affects the patient and the family members in various ways. It is a disorder of cellular differentiation and proliferation that can affect the brain, skin, kidneys, heart and other organs. Many
of the clinical features result from hamartomas, but true neoplasms also occur, particularly in the kidney and brain. Abnormal neuronal migration plays a major additional role in neurological dysfunction. An estimated incidence is one case per 6,000 live births. If individuals who are mildly affected were considered then the rate might be much higher. Approximately 60-70% of TSC cases are thought to result from new mutations. About 30% of normal parents had TSC.

The cutaneous findings are usually the first clue that patient has TSC but other features may lead to diagnosis. Patients with TSC have several typical dermatologic findings. Onset before the age of five years with cutaneous changes or with epilepsy is usual, although the disease may remain latent until adolescence or adult life. Facial angiofibromas are found in 75 percent of affected patients. These lesions appear after 5 years of age and may be mistaken for acne. But these show wide variation in age of onset and severity.
The ash-leaf spot is the earliest skin lesion in patients with TSC. This hypomelanotic macule is most easily visualised with a Wood’s light. About 90 to 96 percent of patients may develop ash leaf spots by the age of 4 yr. By themselves; these macules are not diagnostic of tuberous sclerosis because they are also relatively common in the general population.

The shagreen patch, a thickened orange-peel-textured area of connective tissue hamartoma is most often found on the mid to lower back. This lesion develops in 21 percent of patients with tuberous sclerosis. Shagreen patches may develop between 2 and 6 years of age.

Ungual fibromas are more prominent in adolescents and adults and they are fairly specific to tuberous sclerosis. Patients can also have sublingual or perilingual fibromas. In our case facial angiofibromas were the only cutaneous lesions.

The predominant neurological manifestations of TSC are mental retardation, seizures and behavioural abnormalities. But milder forms have little or no neurological impairment. The classical triad of TSC consisting of skin lesions, mental retardation and epilepsy is said to be present in about one third of patients. The seizures usually start occurring before 2 years of age. Intelligence is normal in one fourth patients with seizures but nearly all mentally retarded patients have seizures. In our case patient and his mother had seizures but brother had no seizures. All the three are mentally sound. Neuropathological lesions of TSC include calcification seen on plain skull X-ray in about 50 percent of patients. CT and MRI findings include periventricular [subependymal] nodules, parenchymal hamartomas [cortical tubers], ventriculomegaly and rarely subependymal giant cell astrocytomas. In our case both patient and his brother had CNS lesions, calcified tubers.

Renal angiomyolipomas occur in up to three fourths of patients with TSC; most of these lesions are histologically benign tumours with varying amounts of vascular tissue, fat, and smooth muscle. The prevalence of renal tumours increases with age, and tumours larger than 4 cm are much more likely to become symptomatic than smaller tumours. Renal cell carcinoma or other malignancies are less common. Single or multiple renal cysts are also a feature of TSC; these tend to appear earlier than the renal tumours. USG or cranial CT easily identifies larger cyst and the combination of renal cyst and angiomyolipomas are characteristic of TSC. In our case both patient and his mother had renal angiomyolipomas.

Lymphangiomyomatosis occurs in 1 to 6 percent of almost exclusively female patients with tuberous sclerosis. So all females at the age of 18 years require evaluation with CT of chest. Spontaneous pneumothorax, dyspnoea; cough and haemoptysis are typical symptoms of pulmonary TSC. Almost two-third of patients with pulmonary TSC die within 5 years of the onset of symptoms. Lung transplantation may be considered in patients with end stage disease.

Cardiac rhabdomyomas occur in 50 percent of patients with tuberous sclerosis. These lesions can be detected by echo cardiographs. Although the rhabdomyomas are frequently asymptomatic, they may cause heart failure in infants because of outflow obstruction of one or both ventricles. Rhabdomyomas decrease in size with age. These lesions are sometimes evident during prenatal ultrasound testing. A few children later develop cardiac arrhythmias or cerebral thromboembolism from the rhabdomyomas. Some patients stabilise after medical treatment and eventually improved; others require surgery.

The frequency of retinal hamartomas in TSC varies from almost negligible to 87 percent of patients. Retinal lesions vary from the classic mulberry lesions adjacent to the optic disc to the plaque like hamartoma

Fig. 6: CT scan brain showing multiple small calcified tubers in bilateral cerebellar hemisphere and bilateral periventricular white matter in cerebral hemisphere

Fig. 7: USG abdomen showing angiomyolipomas in Rt. kidney of the mother
or deep pigmented retinal lesions. Some patients have visual impairment and very few patients have visual loss caused by retinal detachment, vitreous haemorrhage or hamartoma enlargement. Fundoscopic examination is a recommended procedure at the time of diagnosis, to monitor existing abnormalities or for new symptoms. Occasionally, patients have pigmentary defect of the iris. In our study all the three had normal fundoscopy.

**Final Comment**

The dermatologic manifestations of tuberous sclerosis are helpful in diagnosing this disorder. Unfortunately no specific prenatal laboratory test is available. Genetic counselling should be offered to families with affected members, even though accurate counselling remains difficult because of the variability of gene expression.

All the patients diagnosed to have TSC should be evaluated for this by 2-D Echo, ECG, USG abdomen, cranial CT, and CT of the chest. In our case, patient had 3 major features of TSC, mother and brother had 2 major features. There is no cure for TSC, but the symptoms can be treated and/or managed. Surgery, including dermabrasion and laser treatment may be useful for treatment of skin lesions. Seizures are treated with antiepileptic drugs and systemic complications are treated symptomatically. As TSC is a lifelong condition, regular surveillance to look for symptoms and early treatment are associated with better health and quality of life outcomes for people with TSC.

**References**