Case Report

Tuberous sclerosis complex: Role of radiology as an invaluable tool in management and follow-up

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Abstract

Tuberous sclerosis complex is a genetic disorder, which affects many organs in the body manifesting spectrum of symptomatology. The severity of the disease can be gauged from the extent of involvement of a particular system. Since the disease runs a long course from its presentation at childhood till adulthood and hence the monitoring is very important to have some qualitative life. Other than the common symptomatology and a few laboratory tests, radiological investigations ***viz.*** ultrasound, color Doppler sonography, computed tomography and magnetic resonance imaging play a major role in follow-up for the management map road and associated complications. We present a case where a female child had a follow-up from the age of 8 years till 20 years of age. The follow-up and the management were designed mainly as per the radiological findings. The radiological findings have indicated the time for the patient to undergo surgical intervention in addition to the ongoing medical management.

Key words: *Genetic disorder, Radiological investigations, Tuberous sclerosis complex*

Tuberous sclerosis complex (TSC) is also known as Bournville's disease or Epilola. This is a multisystem genetic disorder wrapping signs and symptoms of skin, brain, kidneys and other organs. This has manifested in the form of growth of many non-cancerous tumors (benign) in many parts of the body. It was discovered by French physician Bournville in 1880 [1]. TSC leads to significant health problems due to its multisystem involvement. The incidence is 1 in 6000 in the general population and there is no predilection for any sex.

CASE REPORT

An 8-year-old female first reported to the Pediatric Outpatient Department in 2001 for generalized seizures and mild degree of mental retardation. The child was having multiple reddish papillary lesions as facial angiofibromas in the nose, cheek and chin regions. Other diagnostic findings such as multiple dental enamel pittings, multiple hypomelanotic macules, shagreen patch and multiple ungual fibromas were present. She was admitted in pediatric intensive care unit (PICU) and anticonvulsant therapy was started to control the seizures along with other supportive therapies. The genetic workup and karyotyping has already confirmed the diagnosis of tuberous sclerosis before the patient came to this institute. Further radiological workup was planned to rule out progression of the disease and other systemic involvement. Contrast enhanced computed tomography (CECT) Head has shown a few bilateral sub ependymal and cortical tubers. X-ray chest was unremarkable and ultrasound (US) abdomen showed a few hamartoma of heterogeneous echogenicity in left kidney and inhomogeneity of echo texture in the right kidney.

The child was put on vigabatrin with the initial dose of 30 mg/kg/day divided in three doses and was gradually increased to 80 mg/kg/day. Though, the seizures were controlled but there was progressive increase in mental retardation, behavioral changes and learning problems. At 10 years of age, she complained of diplopia and repeat non-enhanced head CT (NCCT) head showed bilateral sub ependymal periventricular tubers and sub ependymal giant cell astrocytomas (GCA) on left side blocking the foramen of monro leading to hydrocephalus. The hydrocephalus was treated by placing the ventricular - peritoneal (VP) shunt by the neurosurgeon. Follow-up contrast enhanced magnetic resonance imaging (MRI) head, done after a fortnight, had shown considerable improvement (Fig. 1).

At the age of 12 years, the patient was investigated again for abdominal pain and found to have left sided renal angiomyolipoma (AML). At the age of 14 years, the left renal AML has become massive in size. The left kidney was non-functioning as seen in excretory urography (Fig. 2). CECT

abdomen has shown a huge mass replacing the left kidney (Fig. 3). There was development of right sided AML as well but it was of small size. The child was kept in PICU for a fortnight due to multi-organ involvement and intractable seizures. She was managed with Midazolam continuous infusion with 0.2 mg/kg bolus, followed by 0.1 mg/kg/h to control the seizures. She underwent left radical nephrectomy and was put on yearly follow-up. CECT, MRI and magnetic resonance angiography of head on this admission failed to show any new lesions.

In 2013 at the age of 20 years, she was again hospitalized with complaints of abdominal distension, increasing breathlessness and worsening neurological symptoms. Her blood urea was 56 mg/dl and serum creatinine was 2.3 mg/dl. X-ray abdomen showed right sided opaque abdomen displacing the gas shadows while ultrasonography abdomen showed a huge mass in the right renal region and its outline could not be delineated. CECT (Fig. 4) and MRI (Fig. 5) of abdomen have shown that the right kidney was replaced by a mass of in homogenous nature. Glomerular filtration rate has decreased considerably and the nephrology consultation was also taken. There was no venture advocated for the additional treatment

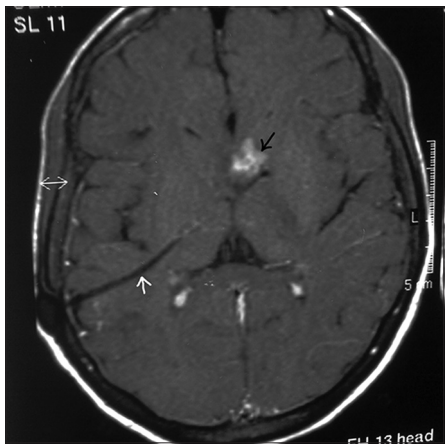

Figure 1: Contrast enhanced T1W magnetic resonance imaging head (2004) axial section after a fortnight of the placement of ventricular - peritoneal (VP) shunt (white arrow). There is no hydrocephalus. VP shunt is seen *in situ*. The enhancing periventricular nodule is also seen in the image (black arrow)

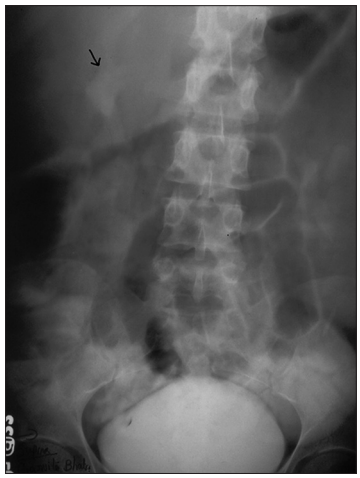

Figure 2: Abdomen X-ray intravenous excretory urography (2007). There is no excretion seen on left side but the right kidney shows excretion with splaying of calyceal system (black arrow)

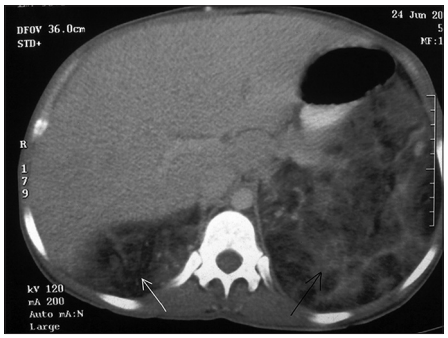

Figure 3: Contrast enhanced computed tomography abdomen (2007) axial section: There is huge mass replacing the left kidney (black arrow). The mass is predominantly of fat constituent with few soft tissue components suggestive of angiomyolipoma (AML). Right kidney also shows a few small AMLs (white arrow)

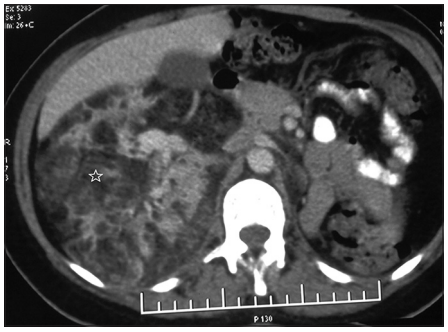

Figure 4: Contrast enhanced computed tomography abdomen (2013) axial section shows a large heterogenous mass suggestive of angiomyolipoma in right renal fossa (white star). Left renal fossa is empty because of earlier total nephrectomy

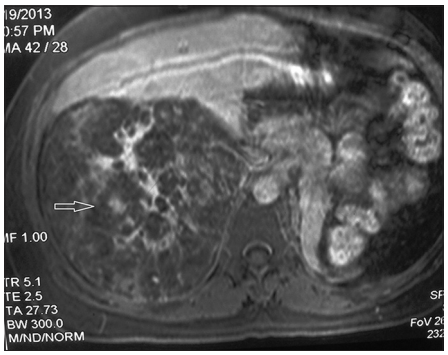

Figure 5: Magnetic resonance imaging abdomen (2013) axial section gradient image with fat sat shows the total replacement of right renal tissue by the fat and other components (white broad arrow). Left renal fossa is empty

keeping in view of the acute on chronic renal failure situation. The breathlessness was treated symptomatically because of the underlying renal impairment. NCCT head has shown multiple calcified foci in the periventricular region. There was no hydrocephalus and the shunt could also be seen in the scan. The functional MRI was planned to earmark the tubers responsible for the seizures and to advise surgery if possible. At present, the patient is mainly under follow-up of both neurologist and nephrologists beside other problems.

DISCUSSION

TSC is a genetic disorder of multidisciplinary involvement with autosomal dominant inheritance. The quality of life is highly affected by this disease because of so many progressive complications involving multiple organs. Mutations in two genes namely TSC1 and TSC2, which act as tumor suppressors, are responsible for various manifestations. TSC1 is related to the protein Hamartin on chromosome 9 (9q34) and TSC2 to the protein tuber in on chromosome 16 (16p13). The individuals of TSC are born with one mutated copy of TSC1 or TSC2. The second mutation must take place in lifetime for the development of some type of tumor in the body [2].

The patients usually develop symptoms before 10 years of age as in our case. The classical clinical Vogt's triad (1908) of seizures, mental retardation and adenoma sebaceum is seen in 30% of the patients. This genetic disorder manifests by growth of numerous non-cancerous (benign) tumors in many parts of the body [3]. Cutaneous lesions are seen in 96% of the cases. Skin shows hypomelanotic macules, confetti lesions, facial angiofibromas, ungual fibromas, shagreen patches and forehead plaques. Facial angiofibromas are reddish papillary lesions on nose, cheek and chin and can be seen in 70% of cases. Pitting of dental enamel can be seen in almost 90% cases of TSC as compare to 9% in general population.

Neurological manifestations may be in the form of seizures (60%), mental retardation (40%), behavioral problems and brain tumors. There may be hyperactivity or aggression and attention deficit disorders. 80% of the cases show calcification which is not common in childhood. Subependymal nodules and GCA can cause various complications even blocking the CSF flow leading to hydrocephalus [4]. The peak incidence is from 8 to 18 years of age. Grey and white matter junctional lesions displace normal cortical tissue leading to abnormalities. 10-15% of subependymal nodules may convert into GCA. The heart, lungs, kidneys, eyes and bones are other organs which can be affected by this order and include cardiac rhabdomyomas, retinal phakomas and lymphangioleiomyomatosis (LAM) causing serious lung complications. Renal cysts in childhood and AML in adults are the common kidney manifestations. 20% of all AML are from this entity. The complications are because of enormous size of the AML with internal bleeding. The lesion can be decreased in size by embolization by interventional radiological procedures. The complications have decreased considerably because of better and advanced management. The bone involvement is in the form of sclerosis of calvaria, spine, ribs, long bones, metacarpals, metatarsals and phalanges. The clinical diagnostic criteria of TSC are of great value [5] in the diagnosis (Table 1).

For the clinical diagnosis following parameters are considered:

- Definite TSC: Either two major criteria or one major with two minor criteria
- Probable TSC: One major and two minor criterion
- Possible TSC: Either one major or two or more minor criteria.

There is great role of radiological investigations in the management and follow-up of TSC. The plain radiograph of chest can reveal early changes in the lungs as these patients can have LAM. US examination picks up the detailed anatomy of the kidneys with the developing tumors or cysts. AML can be characterized as per their size, shape, outline and the extent. There is always need of yearly screening for the kidney lesions. Color Doppler sonography (CDS) can highlight the vascularity of the lesions. CT and MRI are the most sensitive imaging modalities for the diagnosis [6-9]. These further add to the information regarding the functional status of the organs after the contrast study. MRI is performed in the patient on 1-3 years basis irrespective of the patient symptoms. MRI is useful in picking up the cortical and sub-cortical tubers as it has got the property of tissue characterization. These are hyper intense on T1W and hypo intense in younger children. In older children, these tubers become isointense on T1W and hyper intense on T2W [10-12]. Only 10% of the lesions show enhancement. On the other hand, CT is good for elaborating renal lesions and calcification. AML shows hyper intensity on T1W images

Table 1: Clinical diagnostic criteria for TSC

Major features	Minor features
Hypomelanotic macules (>3)	"Confetti" skin
Angiofibroma (>3) or forehead plaque	Dental enamel pits (>3)
Ungual fibromas (>2)	Intraoral fibromas (>2)
Shagreen patch or multiple collagenomas	Retinal achromic patch
Multiple retinal hamartomas	Multiple renal cysts
Cortical dysplasias (>3)	Nonrenal hamartomas
Subependymal nodules (>2)	
Subependymal GCA (>2)	
Cardiac rhabdomyoma	
LAM	
AML (>2)	

GCA: Giant cell astrocytomas, LAM: Lymphangioleiomatosis, AML: Angiomyolipomas, TSC: Tuberous sclerosis complex

and these lesions show signal loss after fat suppression sequences [13,14].

Management depends upon the involvement of the particular system. Primary aim is to control seizures and treatment guidelines are similar as that of epilepsy. The other new drugs used for seizures are topiramate, lamotrigine, oxcarbazepine and levetiracetam, but unfortunately pharmacoresistance is quite common. The alternative treatment for the medical drug resistance cases is in the form of ketogenic/low glycine diet, vagus nerve stimulation and selective surgery for the responsible cortical tubers seen in functional MRI [15]. Supportive treatment is essential part of the management to improve the quality-of-life [16]. 40% of the patients die by 35 years of age. The drug like sirolimus (rapamycin) has been used with a few benefits; however, in our case these drugs were not used.

CONCLUSION

The patients of TSC have got multi-system involvement with progressive course leading to wide spectrum of symptoms. The management has to be tailored in that fashion along with genetic screening and counseling. In addition to the plain radiography, the US, CDS, CT and MRI are invaluable tools in the diagnosis and management guidance. As in the present case, long-term follow-up by radiological investigations helped in the patient management.

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