A Case Series of Tuberous Sclerosis Complex: Clinico-radiological Study and Review of the Literature

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ABSTRACT

Introduction: Tuberous sclerosis complex (TSC) is a relatively rare autosomal dominant disorder characterized by a variety of hamartomatous lesions in various organs. The diagnosis is usually established on the basis of diagnostic criteria related to clinical and/or radiologic findings. Since the classical Vogt triad of seizures, mental retardation, and adenoma sebaceum are seen in only a minority of cases, radiology plays an important role in diagnosis of the disease. The aim of the study is to evaluate the clinico-radiological pattern in this disease. **Materials and Methods:** A clinical and radiological evaluation of 4 cases of suspected TSC was conducted within a period of 18 months. **Results:** All the four patients were below 25 years of age. Two patients were female and two were male. All the 4 patients had a history of seizures, while 2 also had mental retardation. One patient had hypomelanotic macules. On imaging, all the 4 patients showed neurological involvement in the form of cortical tubers, subependymal nodules, and white matter abnormalities while only one patient showed radial migration lines. One patient additionally showed the presence of cardiac rhabdomyoma. **Conclusion:** In addition to clinical examination, imaging plays a very important role in identifying the abnormalities of TSC and other additional features.

Key words: Hypomelanotic macules; rhabdomyoma; tuberous sclerosis; tubers

Introduction

Tuberous sclerosis complex (TSC) is rare autosomal dominant inherited neurocutaneous syndrome, characterized by a variety of hamartomatous lesions in various organs. The estimated prevalence ranges from 1 in 6000 to 1 in 12,000.[1-3] Approximately, 50% of cases are inherited and 50% are sporadic although the incidence of sporadic cases may be as high as 80%.[3,4] The disease is caused by mutations in either the*TSC1* gene, on chromosome 9q34, or the *TSC2* gene, on chromosome 16p13.3.[4-7] It can affect both sexes and all ethnic groups.[8] Manifestations of tuberous sclerosis (TS) can become apparent in persons of any age, but most patients have clinical symptoms before the age of 10 years. Classically, TS demonstrates a triad of clinical features (Vogt triad): mental retardation, epilepsy, and adenoma sebaceum (facial angiofibroma). However, it should be recognized that half of TS patients have normal intelligence and that a quarter does not have epilepsy.[9] On radiological evaluation, intracranial features are the most common and include cortical or subcortical tubers, subependymal nodules, subependymal giant cell astrocytomas (SEGAs), and white matter radial migration lines. Renal manifestations are the second most common finding associated with TSC, with angiomyolipomas (AMLs) occurring in 80% and renal cystic disease in 50% of the patients. Pulmonary involvement, specifically lymphangioleiomyomatosis (LAM), is the third most common cause of TSC-associated morbidity, occurring

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in approximately 35% of female TSC patients.[10] In patients with TSC, cardiac rhabdomyoma is the most common cardiac manifestation often identified *in utero*, infancy, and early childhood.[11] Some other abdominal lesions such as retroperitoneal LAM, perivascular epithelioid cell tumors, and skeletal lesions such as cysts, periosteal new bone formation, and hyperostosis of inner table of calvaria are also associated with the TSC. Diagnosis of TSC is based on diagnostic criteria revised by Roach *et al*.[12] in 1998 which included both objective clinical signs and imaging findings divided into major and minor features.

Major features include facial angiofibromas, hypomelanotic macules, cortical tubers, subependymal nodules, retinal hamartomas, LAM, renal AML, cardiac rhabdomyomas, shagreen patches, ungual fibromas, and subependymal giant cell tumors.

Minor features

Multiple pits in dental enamel, hamartomatous rectal polyps, bone cysts, cerebral white matter radial migration lines, multiple renal cysts, gingival fibromas, confetti skin lesions, and retinal achromatic patches.

A. Definite diagnosis: 2 major/1 major + 2 minor features
B. Probable diagnosis: 1 major + 1 minor feature
C. Possible diagnosis: 1 major/2 or more minor feature.

Materials and Methods

In this study, four cases of suspected TSC referred to the Radiology Department at Subharti Medical College and Associated Chhatrapati Shivaji Subharti Hospital, a Tertiary Health Care Centre of North India, Meerut, within a period of 18 months were evaluated clinically and radiologically. All patients underwent computed tomography (CT) scan of the brain, ultrasonography (USG) of the abdomen, and echocardiography. Magnetic resonance imaging (MRI) of the brain was done in three patients. Fundoscopy and chest X-rays were done as a part of routine investigation. Informed consent was obtained from the parents of all the patients included in the study.

Case reports

Case 1

A19-month-old female child presented with the chief complaints of epilepsy, hypopigmented macules [Figure 1a and b], and delayed developmental milestones since birth.

Magnetic resonance (MR) images showed:

- Multiple subependymal nodules appearing hypointense on T2-weighted images and hyperintense on T1/FLAIR images along the walls of both lateral ventricles [Figure 2]. Subependymal nodule size measuring 9 mm × 6.3 mm was noted in frontal horn of left lateral ventricle just adjacent to the foramen of Monro [Figure 3]. Multiple areas of altered signals in both cerebral cortices with expanded and flattened gyri appearing hyperintense on T2/FLAIR images and hypointense on T1 images [Figures 3 and 4]
- Few radial white matter linear bands were noted in bilateral parietal regions.

Echocardiography revealed a 27 mm × 14 mm mass in the right atrium [Figure 5]. Small 3–4 mm diameter multiple masses are noted along the length of interventricular septum.

A diagnosis of TSC was made using four major features and one minor feature.

Case 2

A 21-month-old female presented with seizures and behavioral disorder (aggression and repetitive behavior).

On MR evaluation, the findings noted were:

- Bilateral subependymal lesion located in bilateral lateral ventricles appearing hypointense on T1/T2 and iso- to hyper-intense on T2 FLAIR images showing blooming on gradient recalled echo suggestive of calcified subependymal nodule [Figure 6a and b]
- Subtle T2 FLAIR hyperintensity with an area of focal blooming in right parietal region depicting right parietal cortical/subcortical tuber with evidence of calcification [Figure 6a and b].

USG of the abdomen, especially done for kidney evaluation showed bilateral multiple renal cysts [Figure 7a-c].

A diagnosis of TSC was made as two major features and one minor feature were present.

Case 3

A 13-month-old male with complaints of seizures, infantile spasms, delayed developmental milestones, and hyperactivity.

Brain imaging revealed:

- CT images show foci of hyperdensity along the subependymal lining of lateral ventricle suggestive of subependymal nodules, multiple cortical, and subcortical hypodensities - cortical tubers and right periventricular calcification [Figure 8a-c]
- Subependymal nodules along the walls of lateral ventricles appearing hypointense on T2/FLAIR images [Figure 9a and b]
- T2/FLAIR images hyperintensity noted in cortical and subcortical region suggestive of cortical tubers [Figure 10a and b]
- Small well-demarcated lesions of intensity similar to cerebrospinal fluid are noted near the lateral ventricle in white matter suggestive of white matter cyst-like lesion [Figure 11].

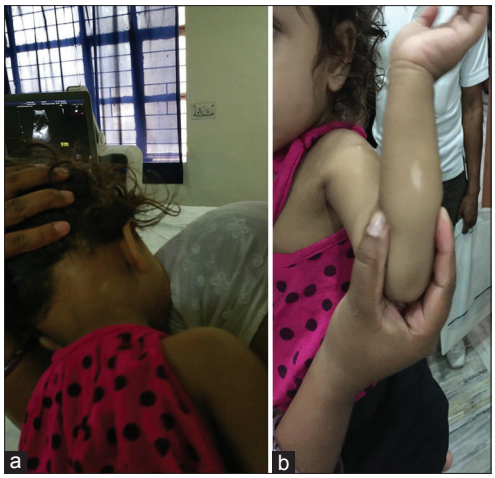

Figure 1: (a and b) Back of neck and forearm showed hypopigmented macules

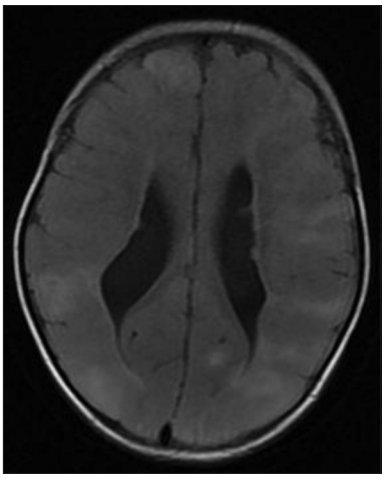

Figure 2: Small hyperintense subependymal nodules along walls of lateral ventricles and multiple hyperintense areas in both cerebral cortices on FLAIR images

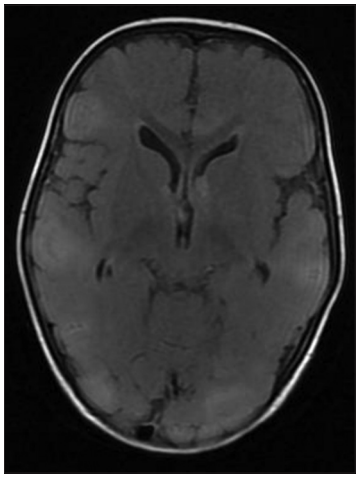

Figure 3: Multiple Flair hyper intense areas in both cerebral cortices

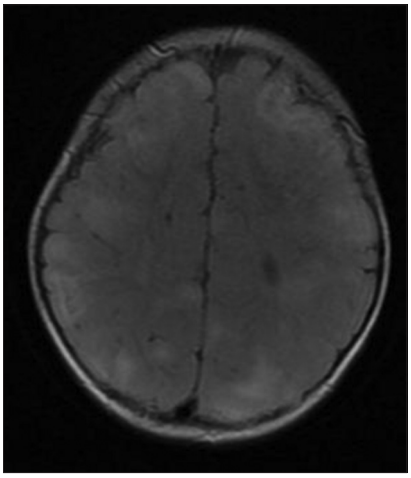

Figure 4: Multiple areas of altered signals in both cerebral cortices with flattened gyri on FLAIR Images

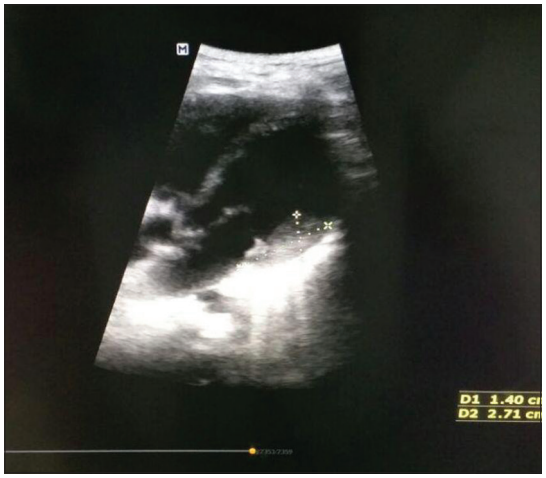

Figure 5: A mass of 27 mm × 14 mm in the right atrium

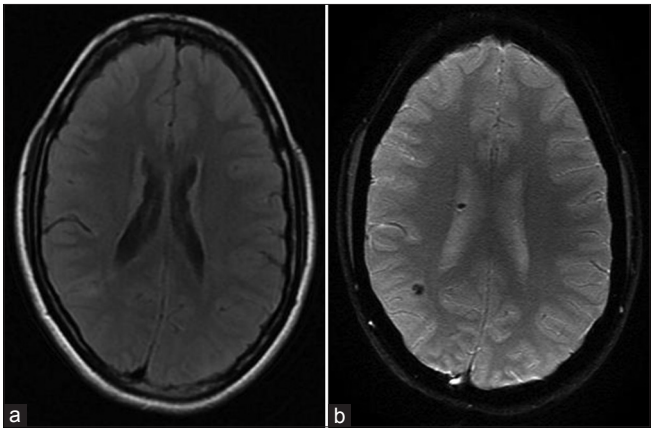

Figure 6: (a and b) Subtle T2 Flair hyper-intensities with areas of focal blooming in right parietal region depicting right parietal tuber with calcification

Fundoscopy of the patient showed evidence of retinal hamartoma [Figure 12].

A diagnosis of TSC was made based on two major features and one minor feature.

Case 4

A 25-year-old male with a history of headache, vertigo, and seizures since 1 year.

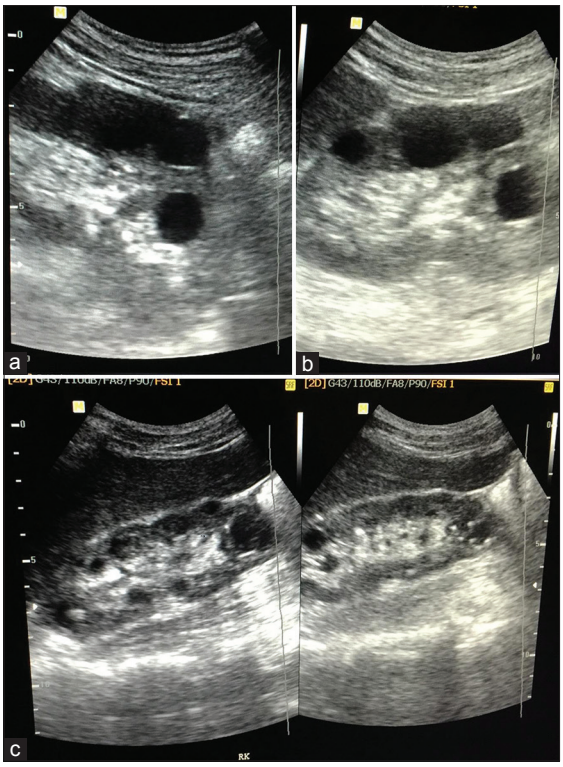

Figure 7: (a-c) Bilateral multiple renal cysts on ultrasonography

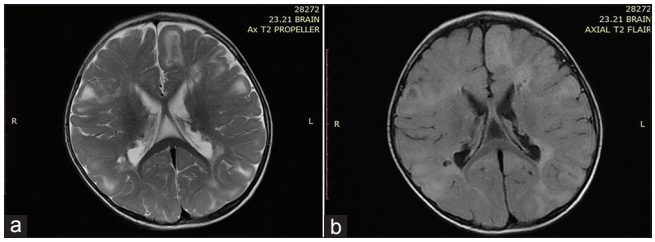

Figure 9: (a and b) Subependymal nodules along the walls of lateral ventricles appearing hypointense on T2/FLAIR image

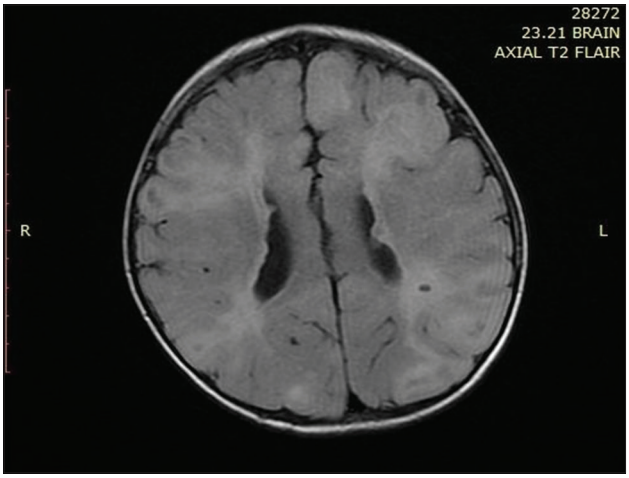

Figure 11: Small well-demarcated lesions of intensity similar to CSF in white matter suggestive of cyst-like lesion

The patient was only subjected to CT which showed:

- An ill-defined lesion of approximate size 32 mm × 22.5 mm with hypodensity within in the midline in the region at foramen of Monro with resultant dilatation of bilateral lateral ventricles suggestive of SEGA [Figure 13a]
- Multiple subependymal small calcified bilaterally [Figure 13b].

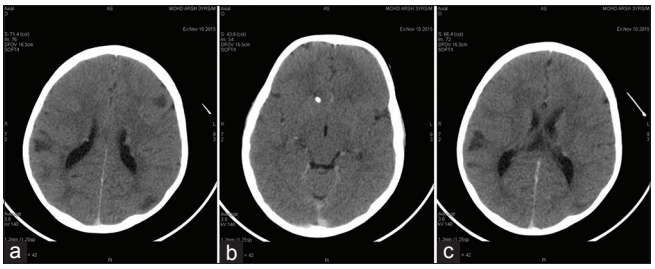

Figure 8: (a-c) CT images show foci of hyperdensity along the subependymal lining of lateral ventricle suggestive of subependymal nodules, multiple cortical, and subcortical hypodensities- cortical tubers and showed right periventricular calcification

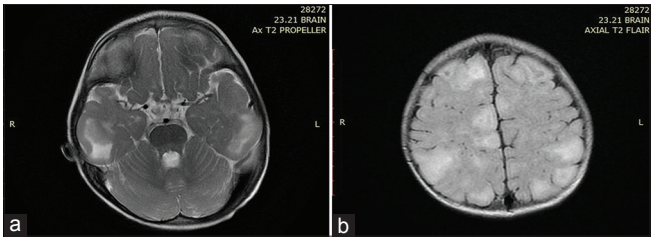

Figure 10: (a and b) Axial image hyperintensity shown in the cortical and subcortical region suggestive of cortical tubers

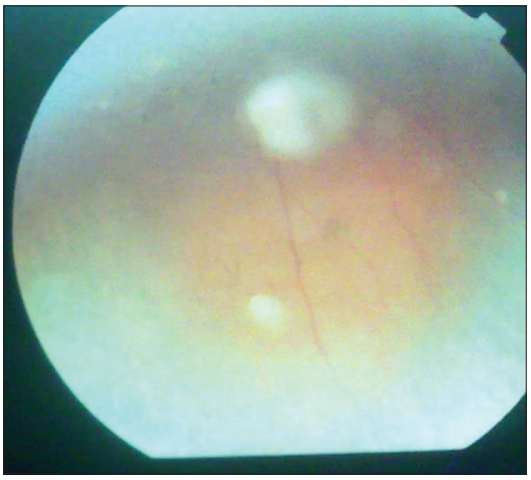

Figure 12: Retinal hamartoma of fundoscopic examination

In view of above findings, the provisional diagnosis of TSC was made.

Discussion

TSC, also referred to as Bourneville-Pringle's disease, is characterized by hamartomas in multiple organs. It presents with a wide range of clinical manifestations, predominantly affecting the skin, brain, kidney, heart, lung, eye, and bone.

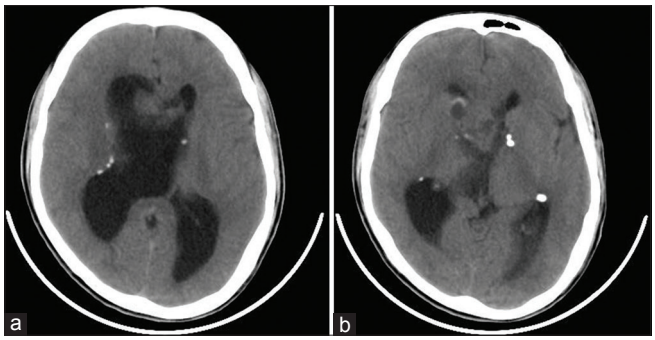

Figure 13: (a and b) Poorly defined hypodense lesion in the midline in the region at foramen of Monro and dilatation of bilateral lateral ventricles, suggestive of subependymal giant cell astrocytoma and multiple subependymal small bilateral calcification

In our study, all patients were under 25 years of age with no sex predilection which is in accordance to the study by Casper *et al*.[13] who did imaging in 59 patients with TSC. They found the mean age of patients at the initial imaging examination was 11.4 years (range, 3 days to 36 years) with no sex predilection. However, this was in contrast to a study by Puri[14] who found that male outnumbered female by a ratio of 2.3:1 in her study, but the age group was from 11 to 20 years only which was in accordance with our study.

CT and MRI findings were reviewed in four patients with TS. All patients underwent CT; three patients underwent both. The CT features included subependymal nodules in four of four patients (100%) and calcifications in three of four patients (75%). Parenchymal hamartomas (cortical tubers) were seen in three of four patients (75%). The MRI characteristics included subependymal nodules (periventricular nodules) of intermediate signal intensity in all the patients. Parenchymal hamartomas demonstrated in three of the three patients (100%), usually exhibited long T1 and T2 relaxation characteristics. These findings were in agreement with the findings of Altman *et al*.[15] who studied the CT and MRI characteristics in TS in 26 patients, with 16 patients undergoing both investigations and rest only CT. The CT features included subependymal nodules in 25 of 26 patients (96%) and calcifications in 23 of 26 (88%). Parenchymal hamartomas (cortical tubers) were seen in 23 of 26 patients (88%). These lesions had less attenuation than surrounding brain in 16 of 26 patients (62%) and were calcified in 14 of 26 patients (54%). Contrast enhancement of a lesion, indicating a SEGA, occurred in three of 26 patients (12%). The MRI characteristics included subependymal nodules (periventricular nodules) of intermediate signal intensity in 10 of the 16 patients (63%). Parenchymal hamartomas demonstrated in 15 of the 16 patients (94%). In addition to these, we also noted radial bands in one of our cases which further strengthened the diagnosis.

In one of the cases, we found multiple renal cysts in both the kidneys. Findings from one previous study[16] showed that the average age at which a renal ultrasound (US) scan became abnormal was 7.2 years, but the case, in which we found

Table 1: Summary of clinical and imaging findings in TSC

CLINICAL FINDINGS	NEUROLOGICAL FINDINGS	ABDOMINAL FINDINGS
• Mental retardation • Autism • Hypopigmented macules • Facial angiofibromas and forehead plaques • Shagreen patches • Periungual fibromas	• Cortical and subcortical tubers • White matter abnormalities • Subependymal nodules • Subependymal giant cell astrocytomas	• Renal angiomyolipomas • Extrarenal angiomyolipomas • Polycystic kidney phenotype • Renal cell cancer • PEComa

CARDIOPULMONARY FINDINGS	SKELETAL FINDINGS	VASCULAR FINDINGS
• Lymphangioleiomyomatosis • Cardiac rhabdomyomas	• Sclerotic lesions	•Pseudoaneurysms in AMLs •Vascular dysplasia (outside AMLs)

Table 2: Major and minor features of TSC

Major Features	Minor Features
Frequent	**Frequent**
Facial angiofibromas	Multiple pits in dental enamel
Hypomelanotic macules	Hamartomatous rectal polyps
Cortical tubers	
Subependymal nodules	
Common	**Common**
Retinal hamartomas	Bone cysts
LAM	Cerebral white matter radial migration lines
Renal AML	Multiple renal cysts
Cardiac rhabdomyomas	Gingival fibromas
Uncommon	**Uncommon**
Shagreen patches	"Confetti" skin lesions
Ungual fibromas	Retinal achromatic patches
Subependymal giant-cell tumors	
Definite diagnosis: two major features or one major feature plus two minor features	
Probable diagnosis: one major feature plus one minor feature	
Possible diagnosis: one major feature or two or more minor features	

bilateral renal cysts were only 21 months old. In contrast to findings of Casper *et al*.,[13] we found renal cysts in one of our cases and AML in none, whereas they found that cysts occurred bilaterally in 61% of patients, which was much < 89% seen with AML in their study.

In a study, it was seen that regarding the clinical spectrum of TS, epileptic fits, and cardiac complications was seen in 50% patients each, eye abnormalities including retinal astrocytomas were seen in 40% patients, mental retardation was seen in 25% patients followed by astrocytomas, and pulmonary disease seen in 20% patients each. While in our

Table 3: Summary of suggested imaging approaches

	Diagnostic checklist	Follow-up interval	Follow-up checklist
BRAIN	•Tubers, SENs, white matter abnormalities, SEGAs	•MRI every 1–3 years; at least yearly if SEGA •Begin serial US examinations at 10 years, sooner if clinically indicated or known TSC2 mutation	•Flow voids; SEGA growth, hydrocephalus •AML and/or cysts bleeding or growth; kidney size
ABDOMEN	•Renal AMLs and cysts •CT scan in females: LAM	•CT scan or MRI for suspected hemorrhage; CT angiography to evaluate aneurysms •Every 3–5 years in women (age more than 18 years) with LAM	•Lesion growth; evaluate renal parenchyma; intratumoral aneurysms >5 mm and/or AAA •Evaluate LAM progression; aneurysms
CHEST	•Echocardiography: rhabdomyoma(s)	•Yearly until involution or stable size	•Involution or stable size

study, 100% of children presented with epilepsy and seizures. Only one patient out of four (25%) presented with retinal hamartoma. None of the patients in our study presented with pulmonary complaints.

In our study, one patient showed cutaneous manifestation in the form of hypopigmented macules or shagreen patches. This is in agreement with findings of Puri[14] who noted that in TS, adenoma sebaceum was the most common (95%) cutaneous feature followed by ash leaf macule and shagreen patch each seen in 90% patients.

In a study by Mühler *et al*.[17] on 21 patients, they found the echocardiographic examination was normal in four and equivocal in three patients, whereas in the remaining 14 cases, echocardiography showed multiple rhabdomyomas in the right ventricle (11) and left ventricle (14) as well as in the right atrium (1). While in our study, we found a mass in right atrium with multiple small masses in the interventricular septum, we did not find any mass in left ventricle in any of our cases on echocardiographic examination.

In our study, the unique findings we found were renal cysts in a very young child of 21 months that is not very commonly reported. Furthermore, we found a mass in right atrium which is rare manifestation as the cardiac masses generally occur in left ventricle.

Follow-up

Patients with TSC should undergo follow-up brain imaging every 1 to 3 years, especially if any lesions have been shown to have grown. The presumed diagnosis of SEGA merits particularly close follow-up, and these children should be imaged each year until age 21 years (then every 2–3 years).[1] The inspection of vascular flow voids should be incorporated into the radiologist's search pattern in TSC because intracranial aneurysms are a rare but important part of this disorder. Surveillance abdominal imaging should consist of a baseline US examination at diagnosis and serial follow-up beginning in the late first decade.[18] Although these scans are often limited to the kidneys, the imager should also briefly inspect the aorta, as there is an increased risk of AAA even in children with TSC.

Similarly, a chest CT scan is often obtained to evaluate LAM in young women with LAM, and a search for aneurysms of the thoracic aorta or pulmonary artery should be made. Most experts recommend that women with LAM undergo a chest CT scan at least every 3 years. Although cardiac rhabdomyomas are asymptomatic, serial echocardiography should be performed until they involute or are shown to remain stable in size. The recommendations for diagnosis and follow-up in TSC patients [Tables 1-3].

Treatment

Therapeutic options for TSC patients revolve mainly around symptomatic management. Vigabatrin is an irreversible GABA inhibitor that has been shown to quell infantile spasms in more than 90% of TSC patients. Older children with particularly epileptogenic focal tubers have been treated by surgical resection.[19] Rapamycin is an immunosuppressant and has caused regression of SEGAs and also shows promise in the treatment of AMLs and LAM.[20] The radiologist should be familiar with these and future treatments because successful treatment will almost certainly change the follow-up imaging.

Conclusion

TSC is a multisystem disorder characterized by a wide spectrum of clinical and imaging features. Recognition of specific radiologic features of various organ manifestations may aid in early diagnosis and management and improve outcomes in TSC patients. Familiarity with the clinical course, sites of potential involvement, and frequency of involvement can allow correct treatment and improvement in quality of life.

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Conflicts of interest

There are no conflicts of interest.

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