

Tuberous Sclerosis Complex Syndrome Cardiovascular and Renal Manifestation of Tuberous Sclerosis Complex and Summary of the Revised Diagnostic Criteria

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Abstract: Tuberous sclerosis complex Syndrome (TSCs) is a dominantly inherited disorder affecting multiple organs; caused by mutations of either the TSC1 or TSC2 gene encoding hamartin and tuberin respectively. It is characterized by the development of benign tumors affecting different body systems. It is important to make an early diagnosis of TSC so that lifelong monitoring, early recognition of complications and proactive treatment can lower the morbidity and mortality rates. We report a case of 3 Month old male infant in India with the features of Tuberous sclerosis complex syndrome like hypopigmented macules (>3), Rhabdomyoma of heart, angiolioma of the kidney, seizures since birth on background of family history of elder sister having (adenoma sebaceum, intractable seizures and mentally challenges since birth) also mother having similar adenoma sebaceum and seizures but due to family background of low economic status has not undergone further workup or evaluation. The central nervous system findings in this young baby were the first to be described, clinical findings of progressively increasing seizure episodes since day 6 of life and there are multiple hypopigmented macules over thigh, back and near axillary region.

Keywords:

1. Introduction

Von Recklinghausen first described tuberous sclerosis in 1862. Desire-Magloire Bourneville (a French physician) coined the term sclerose tubereuse, from which the name of the disease has evolved. Sherlock coined the term EPILEPSIA encompassing the clinical triad of tuberous sclerosis (Epi: epilepsy, Loi: low intelligence, A: adenoma sebaceum).

As the manifestations of the disease are variegated in nature, the term Tuberous Sclerosis Complex (TSC) is now widely used. It is an autosomal dominant neurocutaneous syndrome, characterized by the development of benign tumors such as neurofibromas and angioliomas located anywhere in the body (skin, central nervous system, heart, kidneys etc).

Patients with TSC present mutations of the TSC1 and TSC2 genes, which intervene in cell cycle regulation. This is a dominant autosomal hereditary disease, though 60-70% of all cases are the result of spontaneous mutations.

Tuberous Sclerosis Complex manifests with variable signs and symptoms together with angioliomas distributed in a characteristic "butterfly" pattern on the face and forehead. The most important neurological problems are mental retardation, seizures, autism and learning difficulties.

Cardiac rhabdomyomas are hamartomatous growths or benign tumors composed of cardiac myocytes, and they represent the classic neonatal manifestation of cardiac disease in TSC.

Diagnostic Criteria to diagnose TSC.

Clinical diagnostic criteria

<u>Major features</u>	<u>Minor features</u>
1. Hypomelanotic macules (≥ 3 , at least 5-mm diameter)	1. "Confetti" skin lesions
2. Angioliomas (≥ 3) or fibrous cephalic plaque	2. Dental enamel pits (>3)
3. Ungual fibromas (≥ 2)	3. Intraoral fibromas (≥ 2)
4. Shagreen patch	4. Retinal achromic patch
5. Multiple retinal hamartomas	5. Multiple renal cysts
6. Cortical dysplasias*	6. Nonrenal hamartomas
7. Subependymal nodules	
8. Subependymal giant cell astrocytoma	
9. Cardiac rhabdomyoma	
10. Lymphangiomyomatosis (LAM)	
11. Angiomyolipomas (≥ 2)	

2. Case Report Findings

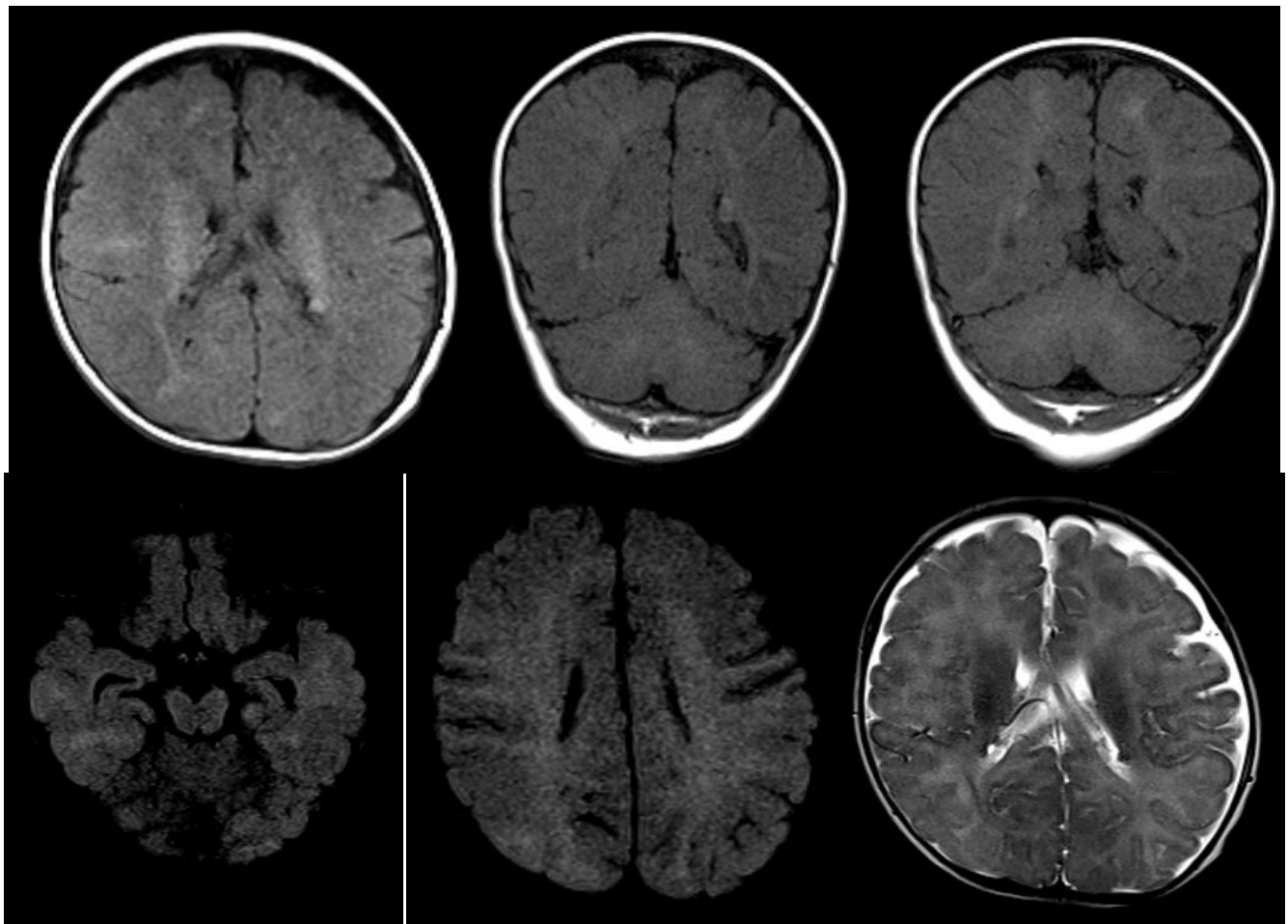
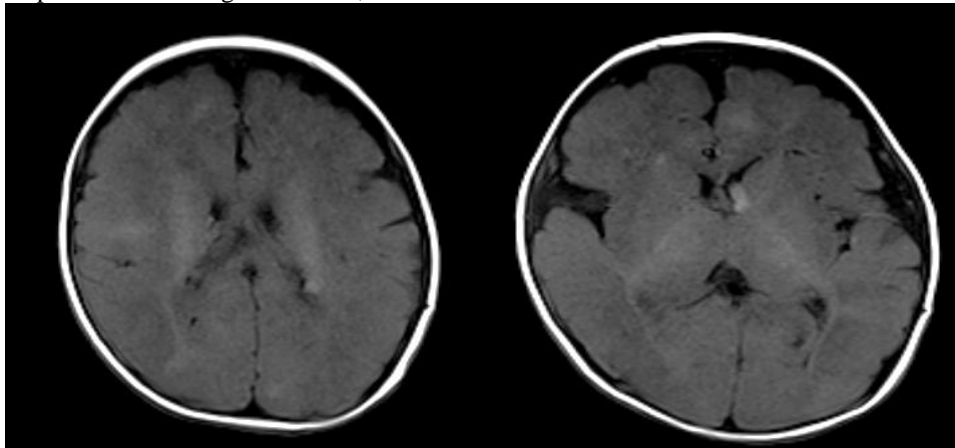
We herein report a case of 3 month old male infant who presented with seizures since 6th day of birth, hypopigmented macules (>3), Rabdomyoma of heart and angioliopoma of the kidney which on further evaluation by MRI Brain showed >3 major features of subependymal nodules, cortical tubers and radiating white matter hyperintensity on T1WI.

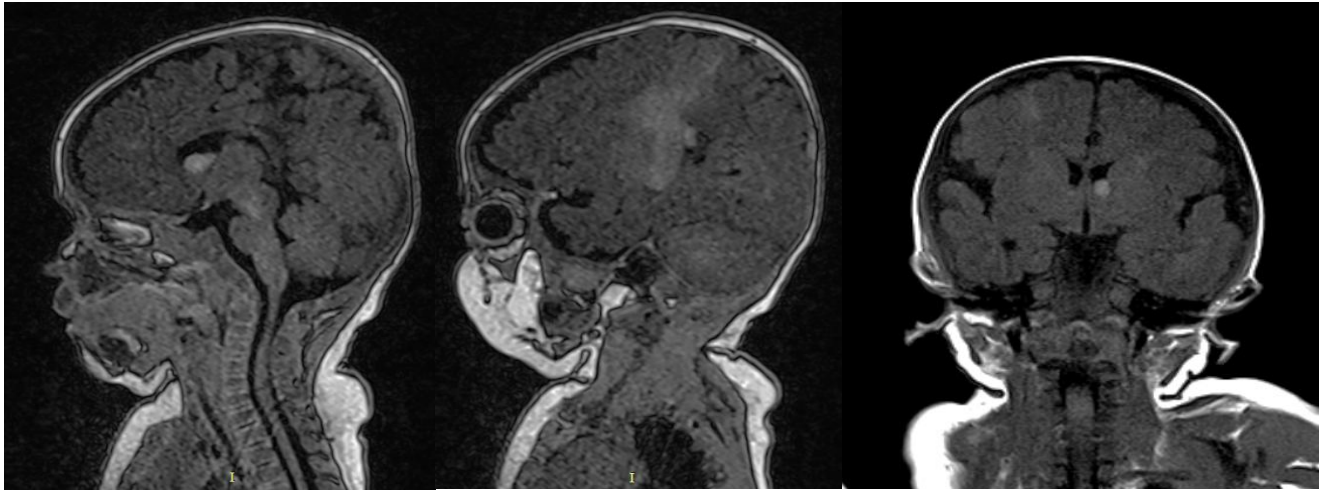
3. Discussion

Tuberous sclerosis is a rare syndrome with an estimated incidence varying from 1 in 20,000 to 1 in 150,000 and the incidence has been reported to be as high as 1 in 10,000.

Patients with Tuberous sclerosis complex (TSC) range from intellectually normal to severely mentally retarded. TSC is often associated with mental retardation (in 70% of cases) and epilepsy (90%). Seizures are the most common neurologic symptom of TSC occurring in 92% of patients.

Thickened cortex with focal areas of predominantly FLAIR hyperintensity and T1WI isointensity and T2WI hyperintensity are noted in both frontal, parietal and occipital lobes with gyral swelling. Tiny subependymal nodules are seen in both lateral ventricle which appears isointense on T1WI and Hypointense on T2WI.



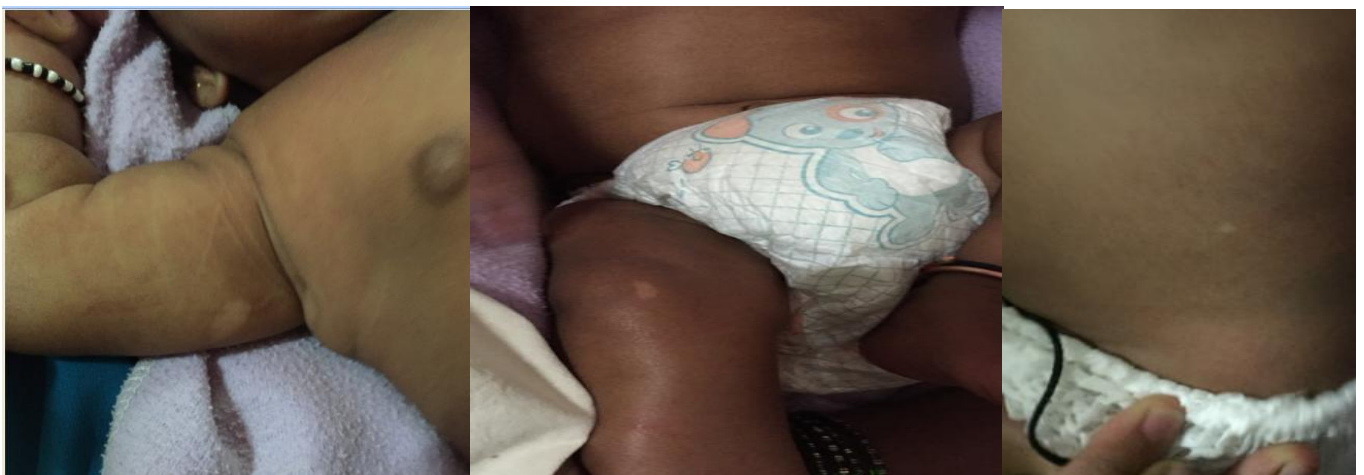


Neurologic symptoms and complications due to the development of cortical tubers, subependymal nodules and subependymal giant cell astrocytomas (SEGA) are common in patients with TSC as we found subependymal nodules and cortical tubers on MRI brain scan.

Most important hamartomas are cerebral cortical tubers, which are regions of abnormal cortical architecture with distinctive large neuronal cells. Cortical tubers cause some

of the most important clinical manifestations of tuberous sclerosis complex syndrome.

Tuberous sclerosis complex is characterized by neurocutaneous manifestations and a careful skin examination of patients suspected to have TSC is mandatory.



(As revealed in the study of Jozwiak et al, the frequencies of patients with hypopigmented macules, facial angiofibromas, forehead or scalp plaque, shagreen patch and periungual fibroma were 97%, 75%, 48%, 19% and 15% respectively.)

Two types of renal lesions occur in patients with tuberous sclerosis: angiomyolipomas and renal cysts. They may be found independently or together they may be unilateral, bilateral, single or multiple. Angiomyolipomas are benign immature and asymptomatic but spontaneous rupture and subsequent hemorrhage in the retroperitoneum may occur and are the cause of chronic renal failure that may prove fatal.

Our case reported with angiomyolipomas of the Left Kidney.

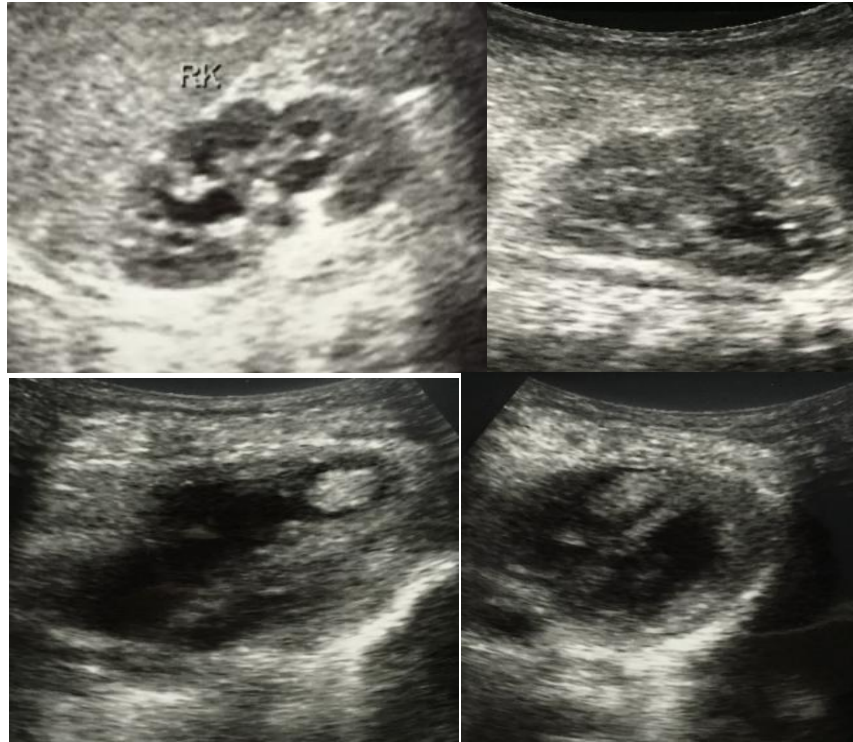
In the heart, the most frequent and characteristic type of tumor is cardiac rhabdomyomas. Incidence of cardiac rhabdomyomas in children with tuberous sclerosis is higher than in adult patients with tuberous sclerosis.

It has been suggested that such lesions tend to regress in early infancy and adolescence and are normally observed before age 25 years in 30-50% of all cases, and are also a cause of early death. Our case reported had rhabdomyoma in wall of right ventricular.

USG: screening of abdomen showed an echogenic lesion in lower pole of left kidney showing contour bulge likely to be angiomyolipoma.

Up to 80% of adult patients with TSC will develop angiomyolipoma.

Our case reported with epilepsy since birth (6th day of life), hypomelanotic macules and (USG screening showed round to oval echogenic lesion in right ventricular myocardium suspicious of rhabdomyoma and echogenic lesion in lower pole of left kidney suspicious of angiomyolipoma.)



4. Conclusion

This case report is a good example of complex nature of tuberous sclerosis. Our case report showed infantile spasms and hypo arrhythmia are more severely affected than those with any other form of epilepsy. The aim of this report is to present various clinical and radiological features of a young

male infant with tuberous sclerosis who exhibited multiple hamartomas of various organ system. Tuberous sclerosis is a rare neurocutaneous syndrome exhibiting multiple hamartomatous proliferations that may involve multiple organ system such as brain, kidney, heart, lungs, eyes and skin.

Surveillance and Management Recommendations for Newly Diagnosed or Suspected TSC Summary Table

Organ System or Specialty Area	Recommendation
Genetics	<ul style="list-style-type: none"> • Obtain 3-generation family history to assess for additional family members at risk of TSC • Offer genetic testing for family counseling or when TSC diagnosis is in question but cannot be clinically confirmed
Brain	<ul style="list-style-type: none"> • Perform MRI of the brain to assess for the presence of tubers, subependymal nodules (SEN), migrational defects, and subependymal giant cell astrocytoma (SEGA) • Evaluate for TSC-associated neuropsychiatric disorder (TAND) • During infancy, educate parents to recognize infantile spasms, even if none have occurred at time of first diagnosis • Obtain baseline routine electroencephalogram (EEG). If abnormal, especially if features of TAND are also present, follow up with a 24-hour video EEG to assess for subclinical seizure activity
Kidney	<ul style="list-style-type: none"> • Obtain MRI of the abdomen to assess for the presence of angiomyolipoma and renal cysts • Screen for hypertension by obtaining an accurate blood pressure • Evaluate renal function by determination of glomerular filtration rate
Lung	<ul style="list-style-type: none"> • Perform baseline pulmonary function testing (PFT and 6-minute walk test) and high-resolution chest computed tomography (HRCT), even if asymptomatic, in patients at risk of developing lymphangioleiomyomatosis (LAM), typically female patients 18 years or older. Adult male patients, if symptomatic, should also undergo testing • Provide counsel on smoking risks and estrogen use in adolescent and adult female patients
Skin	<ul style="list-style-type: none"> • Perform a detailed clinical dermatologic inspection/examination
Teeth	<ul style="list-style-type: none"> • Perform a detailed clinical dental inspection/examination
Heart	<ul style="list-style-type: none"> • Consider fetal echocardiography to detect individuals with high risk of heart failure after delivery when rhabdomyomas are identified via prenatal ultrasound • Obtain an echocardiogram in pediatric patients, especially if <3 years old • Obtain an ECG in all ages to assess for underlying conduction defects
Eye	<ul style="list-style-type: none"> • Perform a complete ophthalmologic evaluation, including dilated funduscopy, to assess for retinal lesions and visual field deficits

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