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CASE SERIES

Case series on tuberous sclerosis

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ABSTRACT
Tuberous Sclerosis Complex is a rare genetic disorder inherited in autosomal dominant fashion caused by mutations on either of two genes TSC1 and TSC2 encoding hamartin and tuberin respectively. It is a multisystem disorder involving brain, skin, kidneys, heart, eyes and lungs which becomes apparent only in late childhood, limiting the usefulness of early diagnosis in infancy. Here we present a case series of patients with tuberous sclerosis highlighting the clinical features, diagnostic challenges and management strategies. Here, we identified 3 patients aged 3, 5 and 14 years in our tertiary care center .The most common clinical features were seizure, skin lesions and subnormal intelligence. Imaging studies revealed cortical tubers and sub ependymal nodules.
TS is a complex disorder requiring multidisciplinary care. Our case series highlights the importance of early recognition genetic counseling and individualized management to reduce morbidity and improve patient outcome.
Key words: Tuberous sclerosis, Subependymal Nodules, Hamartin, Tuberin

INTRODUCTION

Tuberous sclerosis complex (TSC) or Bourneville's disease, first described by Desire-Magloir Bourneville in1880,is a rare genetic disorder of autosomal dominant inheritance with the prevalence of1 in 6000 live birth, affecting both sexes and all ethnic groups.[1,2]Desire-MagloireBourneville(aFrench physician) coined the term sclerose tubere use from which the name of the disease has evolved. Sherlock coined the term EPILOIA encompassing the clinical triad of tuberous sclerosis (Epi: epilepsy, Loi: low intelligence, A: adenoma sebaceum. This disorder is caused by mutation in either the TSC1 or TSC2 gene which encode for protein involved in cell growth and proliferation.

It is a multisystem disorder, and its clinical features are highly variable. Patient may present with a range of symptoms, including seizure, skin lesions, cognitive impairment, Autism spectrum disorder and renal dysfunction. The diagnosis of TS is based on a combination of clinical criteria, imaging studies and genetic testing.

Despite its rarity, TS is an important condition to recognize, as early diagnosis and management can significantly improve patient outcomes. In this case series, we present 3 patients with TS, highlighting the clinical features, diagnostic challenges and management strategies. Our aim to raise awareness about this complex disorder and promote better understanding and care for individuals affected by TS.

CASE REPORT 1

This was a 3 year old female child who presented with seizures for last 2 years. The child was taking multiple anticonvulsants in inadequate doses. On detailed history, the seizures were like myoclonic jerks. The child had delayed motor,social and cognitive milestones. There was no history of head trauma, fever, ear discharge, vomiting and loose motions etc. Except seizures the child did not have any symptoms relevant to heart, kidney, eyes and lungs. There was no family history of seizures.On detailed examination, the child had mild pallor. The child had brown colour maculopapular lesions on face known as adenoma sebaceum (Fig3),5hypopigmented skin lesions on lower back, left buttock and trunk and abdomen (Fig.1). Also a roughened, raised lesion with an orange peel consistency (shagreen patch) was seen on right lower back (Fig.2). It was a home delivery born after consanguinous marriage. Antenatal and perinatal history was uneventful. Immunization and dietary history were satisfactory. Child used to have myoclonic jerks during examination. Detailed systemic examination and fundus examination did not reveal any abnormality. The child was subjected to investigations.Hemoglobin was 8gm/dl.The peripheral smear depicted normocytic normochromic type of anemia. Blood sugar serum calcium, phosphorous, liver function and renal function tests were all with in normal limits. CXR was normal. .MRI brain revealed multiple tubers in the cerebral hemispheres located in

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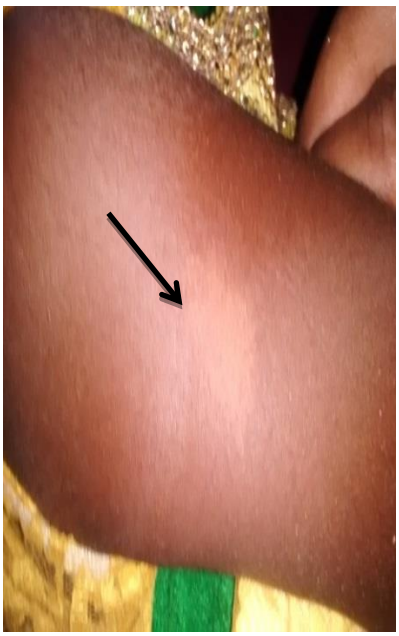
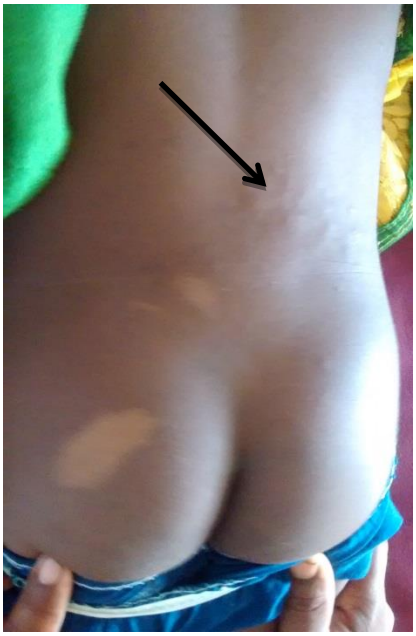
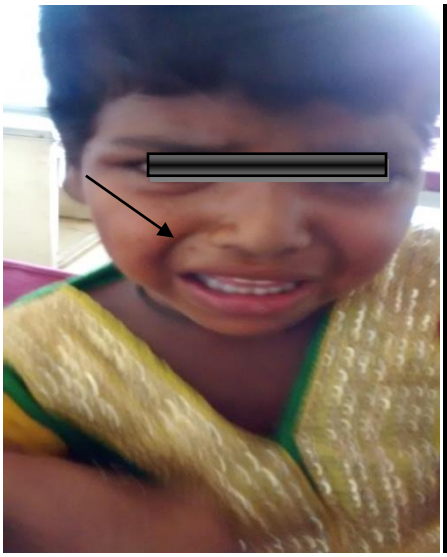
convolutions in subependymal region projecting into the ventricular cavity producing a candle dripping appearance(Fig.4).The echocardiography and ultrasonographic examination of abdomen and KUB region were also within normal limits. EEG revealed hypsarrthymic pattern. In view of clinical history,examination, MRI Brain and EEG, the child was diagnosed as a case of Tuberous sclerosis. Besides maintaining the nutritional status, hematinics, anticonvulsants in form of sodium valproate and vigabatrin were prescribed. The frequency of seizures declined. Child discharged after 5days in satisfactory conditions and regularly followed in pediatric OPD.



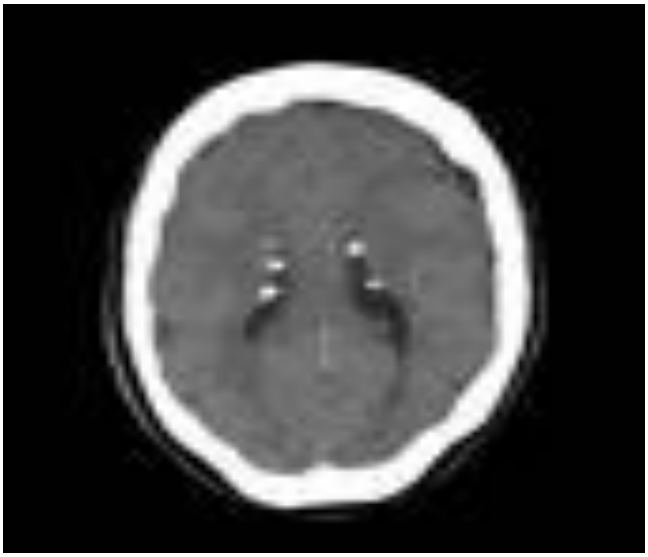
(Figure 1)
Ash leaf macule



(Figure 2)
Shagreen patch and ash leaf macules



(Figure 3) Adenoma sebaceum



(Figure 4) Candle dripping appearance

CASE REPORT 2

A 5 year old male, product of non consanguineous marriage presented to the hospital with complaint of repeated episode of generalised tonic clonic convulsion for 4-5 days, each lasting for around five minute, regained consciousness in between. The convulsions were associated with urinary incontinence, frothing, and uprolling of eye balls. There was no preceding history of fever, cough, diarrhoea or head trauma. He was then started on infusion of Sodium Valproate which controlled the seizures. Past history was not significant.The child had delayed mental and motor milestones. Physical signs included pallor, facial angiofibroma and 4 hypomelanotic macules (Figure-1,2) in lower abdomen, right lower limb,left lower back and epigastric region. A Shagreen patch (Figure-3) was noticed in the lower left back. Investigations like

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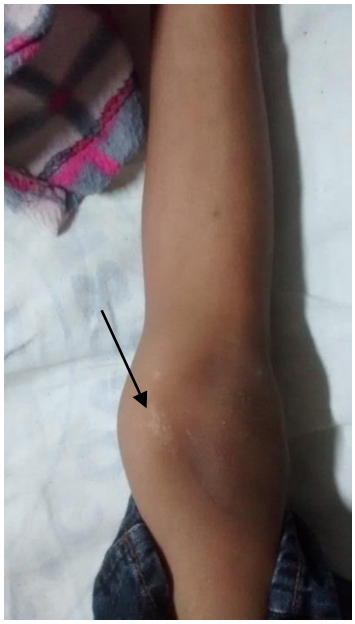
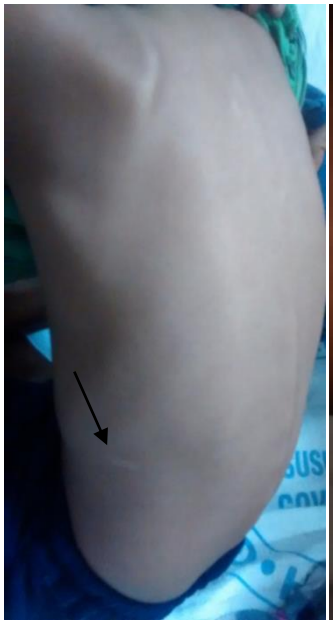
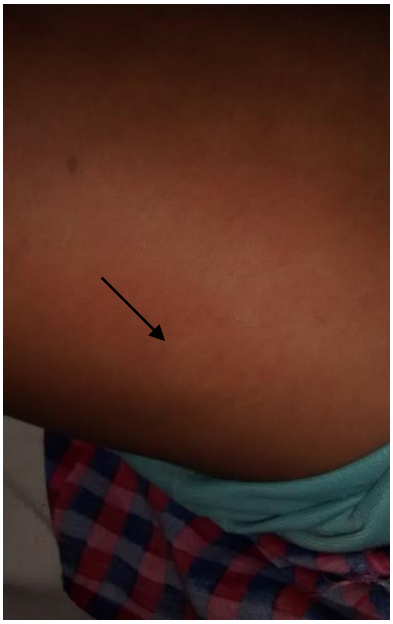
serum electrolytes, blood counts all were within normal limits. C.T. brain without contrast was done, which showed small nodular protrusions into the lateral ventricles with calcified foci, representing subependymal nodule (Figure- 4)

Our patient had four major criteria (subependymal nodule in CT scan head, facial angiofibroma, hypomelanotic macules more than three in number, Shagreen patch) which fit in the diagnosis of Tuberous sclerosis. He had intractable seizure needing frequent adjustment of antiepileptic drug. During this admission, dose of antiepileptic drugs (sodium valproate and carbamazepine) were adjusted accordingly with control of seizure. Child discharged after 6 days in satisfactory condition and regularly followed in pediatrics OPD.

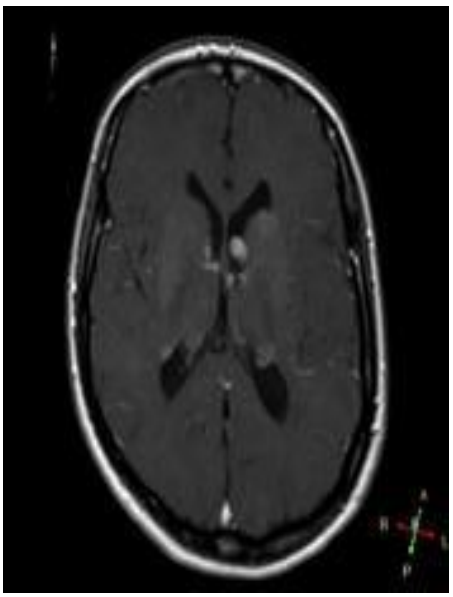




Ash leaf macules (Figure 1,2)



Shagreen patch (Figure 3)



Cortical tuber (Figure 4)

CASE REPORT 3

A 14 year old male boy presented with history of multiple episodes of generalized tonic-clonic seizure for the last 10 days. In past, he had multiple hospital admissions for the same reason and was on antiepileptic drug irregularly since the age of one year with poor control. He was born of non-consanguineous marriage with uneventful birth history with below average scholastic performance. There was no history of seizure in family members; however his father had skin nodules over the face and neck along with 2hypopigmented macules over the trunk.

On detailed examination, the patient had multiple hyper-pigmented papules dark brown coloured of about 5-10 mm size, seen over nose, nasal bridge and

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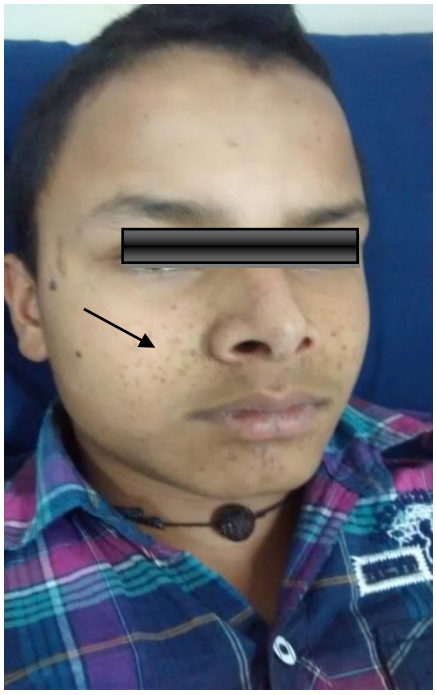
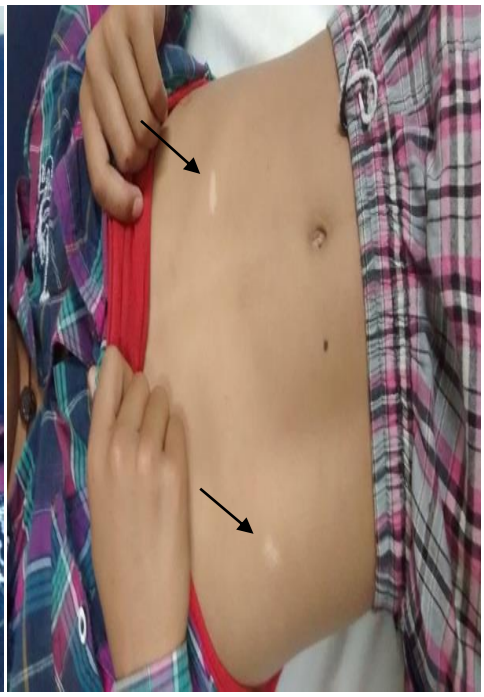
nasolabial region extending to the cheek region in butterfly like distribution suggestive of facial angiofibromas ("adenoma sebaceum")(Fig.1).He also had multiple(five) hypo-pigmented macules (ash leaf) over abdomen (Fig.2) and trunk and along with a thick leathery skin area like an orange peel consistency over the medial malleolus of the left leg suggestive of Shagreen patch(Fig.3). Detailed CNS examination revealed increased tone of both upper and lower limbs with brisk deep tendon reflexes and bilateral positive Babinski's sign but absent superficial reflexes. Other systemic examination and fundus examination revealed no abnormality.

A provisional diagnosis of Tuberous Sclerosis Complex Syndrome was established and radiological investigations were performed. Contrast CT Scan study report of our case showed a solitary hypodense area measuring about 5x5 mm in size seen in axial section**,** suggestive of **'**Subependymal calcification or nodules. CT Scan of the kidney showed multiple cystic hypodense areas suggestive of 'angiomyolipomas (Figure 4)'other test like complete blood count, renal and liver function tests were normal.

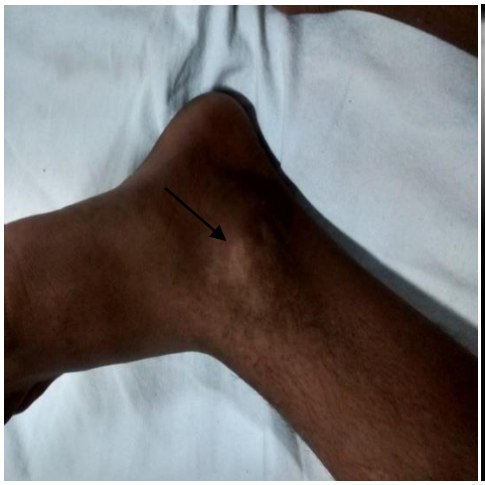
We managed the patient symptomatically. Anticonvulsants in form of sodium valproate and vigabatrin were prescribed. The frequency of seizures declined and patient was discharged after 7 days and advised to be followed biweekly in pediatrics OPD.



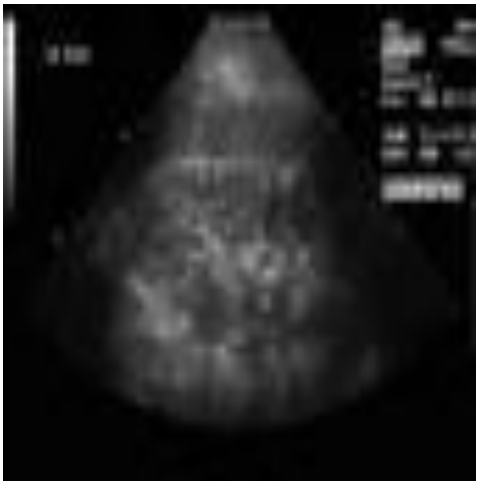
Adenoma sebaceum (Figure 1)



Ash leaf macules (Figure 2)



Shagreen patch (Figure 3)



Angiomyolipoma (Figure 4)

DISCUSSION

It is an autosomal dominant neurocutaneous syndrome, characterized by the development of benign tumors such as neurofibromas and angiofibromas located anywhere in the body (skin, central nervous system, heart, kidneys etc). Patients

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with TSC present mutations of the TSC1and TSC2 genes, which intervene in cell cycle regulation.

The major neurological manifestations of tuberous sclerosis complex are seizures, autism, developmental delay and behavioral and psychiatric disorder. Seizure is present in about 80-90% of patient which begins during the first year of life; varies from subtle focal seizure, infantile spasm, to generalized seizure.[1,5] Seizures are managed with an anticonvulsant medication like Vigabatrin (infantile spasm), Lamotrigine (generalized seizure).[2] But young children with TSC who have early onset of focal seizure or spasm, develops intractable seizure later that responds poorly to antiepileptic drug[1]. Those are candidates for alternative non-pharmacological treatment which includes vagus nerve stimulation, use of ketogenic diet, and resective epileptic surgery.[6]

TSC has dermatologic manifestations like hypomelanotic macule (90%), facial angiofibromas (75%), Shagreen patch (20-30%).[2] Hypomelanotic macules are present at birth and almost all lesions are evident within the first two years of life. Facial angiofibromas (adenoma sebaceum) are present during preschool years in the malar area as small pink to red dome-shaped papules in a "butterfly distribution". The shagreen patch is found in the lumbosacral region characteristically present as an irregularly shaped roughened raised lesion with orange peel consistency. Adolescent pediatric children may have cosmetic issues, so recent trial support the use of topical 0.1% Rapamycin on facial angiofibromas.[7] Use of Inhibitors of the mammalian target of rapamycin (mTOR) in regression of astrocytomas, angiofibromas and angiomyoliomas are newer modalities in the management of tuberous sclerosis.[8]

As revealed in the Journal of Medical Education & Research, Vol. 3, No.1, Jan-July 2013 *Bijjargi S.C. et al* 61 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.[9]

As multiple organs are involved, there is wide variability in presentation. Arguably the 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. 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.[10]

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[10]

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

Diagnostic Criteria[12]for TSC is as given in the table below. Definite TSC can be made when two major or one major plus two minor features are demonstrated

Table 1: Major and Minor Criteria of tuberous sclerosis complex

Major Criteria	Minor Criteria
1. Facial angiofibroma or forehead plaque	1.Multiple dental pits
2. Ungual or periungual fibroma (nontraumatic	2.Gingival fibromas
3. Hypomelanotic macules(>3 and atleast 5mm in diameter	3. Bone cyst
4. Shagreen patch	4.Cerebral white matter migration lines
5. Cortical tuber	5.Retinal achromatic patch
6. Subependymal nodule	6.Confetti skin lesions
7. Subependymal giant cell astrocytoma	7.Nonrenal hamartomas
8. Multiple rentinal hamartomas	8.Multiple renal cysts
9. Cardiac rhabdomyoma	9.Hamaromatous rectal polyps
10 Renal angiomyolipoma	
11. Pulmonary lymphangioleimyomatosis	

CONCLUSION

Our case series highlights the diverse clinical presentations and the diagnostic challenges of tuberous sclerosis. We emphasize the importance of early recognition and multidisciplinary management to improve patient outcomes.

Genetic testing is essential for confirming the diagnosis and identifying familial cases.

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Imaging studies, particularly MRI are crucial for detecting and monitoring tumour growth. TSC is a lifelong condition, therefore individuals should be regularly monitored by an experienced clinician.The quality of life depends on the neurological manifestation like seizures and mental retardation which is improved by multidisciplinary approach and symptomatic organ specific treatment. TSC must be included in the differentials of children presenting with seizures, developmental delay, and mental retardation.

Management should focus on controlling symptoms ,preventing complications and improving quality of life..Further research is needed to elucidate the pathogenesis of TS and developed targated therapies.

To conclude any child who presents with seizures with intellectual disability must be looked for skin lesions which can give some clue towards the causation of seizures.

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