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Case Study

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TUBEROUS SCLEROSIS COMPLEX: CLINICAL PRESENTATION AND DIAGNOSIS

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ABSTRACT

Tuberous sclerosis complex (TSC), also known as Bourneville -Pringle disease is a neurocutaneous syndrome (phakomatosis) inherited in an autosomal dominant manner and have a prevalence of 1 in 6000 newborns. It is characterized by a classic clinical triad known as Vogt's triad which consists of facial lesions (adenoma sebaceum), seizure and mental retardation. Sign and symptoms vary widely, depending on where the growths develop and how severely a person is affected. Here, we report one such case of neurocutaneous syndrome, later diagnosed as tuberous sclerosis complex who presented to us with a history of multiple episodes of seizure.

KEYWORDS: neurocutaneous syndrome, seizure, tuberous sclerosis.

INTRODUCTION

Tuberous sclerosis complex(TSC), also known as Bourne-ville disease or Bourneville-Pringle disease is a neurocutaneous syndrome (phakomatosis) inherited in an autosomal dominant manner and have a prevalence of 1 in 6000 newborns.[1] It is a distinct clinical entity for approximately 125 years since Desiree Magloire Bourneville described the first case in 1880. It is characterized by a classic clinical triad known as Vogt's triad which consists of facial lesions (adenoma sebaceum), seizure and mental retardation, which occurs in only 29% of the patients and 6% lack all three of the characteristics.[2] The disorder can cause a wide range of potential signs and symptoms and is associated with the formation of benign tumours in various organ systems of the body. These tumours are often referred to as hamartomas. Epilepsy affects 80-90 percent of cases and presents either in the form of infantile spasms or simple or complex partial seizures. Electroencephalogram is positive in 75% of the patients.[3] Cognitive deficits occur in 44-65 percent of cases. Features of autism and behavioural problems may be seen in such patients.[4]

Tuberous sclerosis results from alterations (mutations) in a gene or genes that may occur spontaneously (sporadically) for unknown reasons or be inherited as an autosomal dominant trait. There may be a positive family history in 7-40 percent of cases.

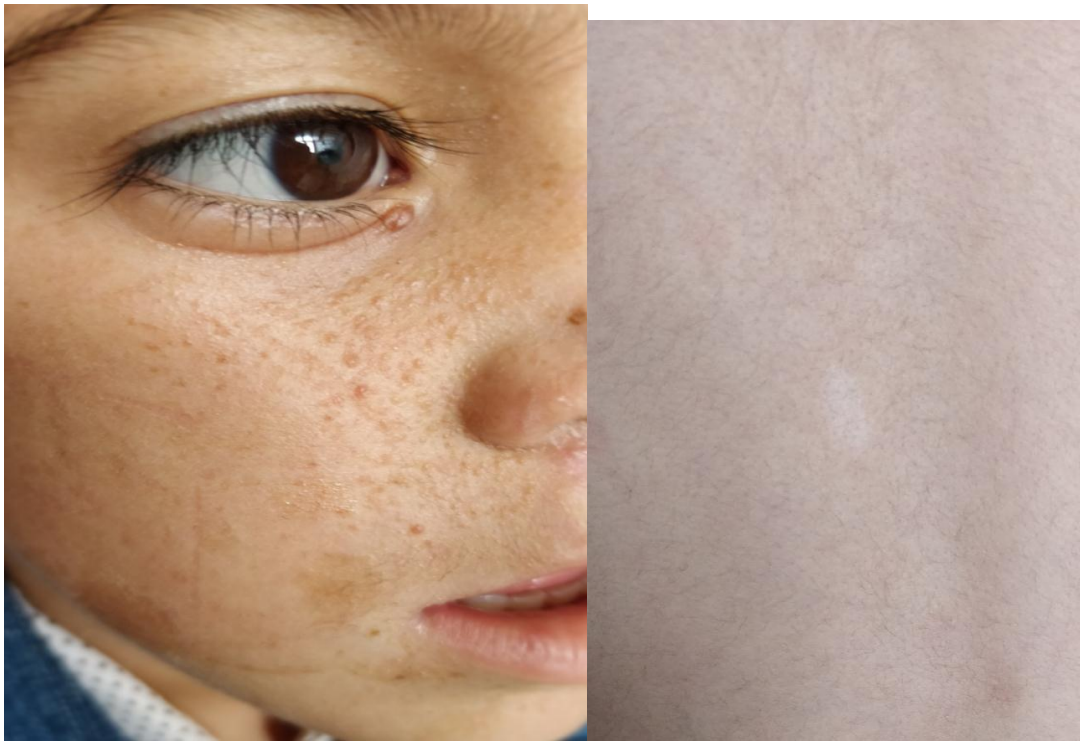
Here we present the case of a 7year old child who had TSC with multiorgan involvement.

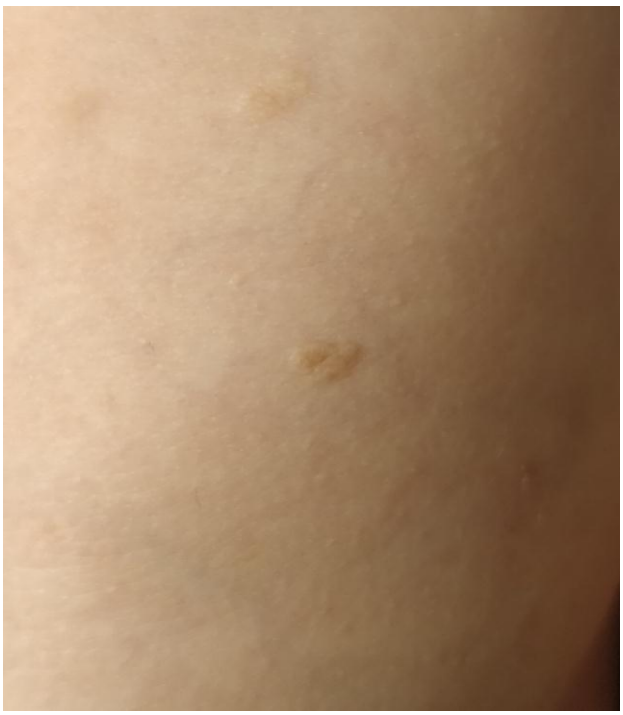
CASE REPORT

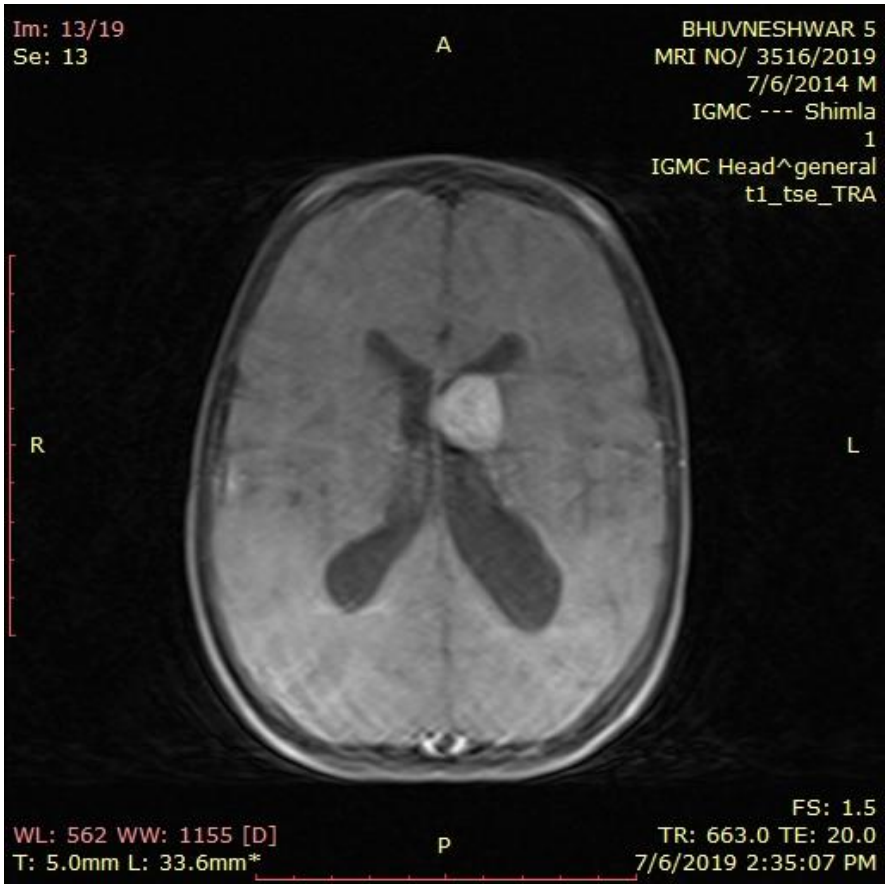
A 7 yr old presented to the paediatrics department of our hospital with the complaints of abnormal body movements since the age of 4yrs. These body movements were previously diagnosed as generalized tonic clonic seizures (GTCS). Since 6yrs of age, he had developed sudden drop of head and the body with drooping of eyelids which was suggestive of the diagnosis of atonic seizures. Gradually the frequency of GTCS increased from 1episode per month to 5-6 episodes per day. He also was found to be developed atonic seizures which occurred every 30minutes. His birth history was found to be uneventful. There was a positive family history of seizures. His mother had a history of developing GTCS since 15 years of age. The child had a history of delayed milestones (DQ=50%). On physical examination, the vitals of the child were stable. There were multiple red nodules over the nose and cheeks. Also there were 3-4 hypo pigmented macules in the lower abdomen, lumbar area and the extremities. There was a small multiple round papular fleshy lesion in the lumbar area. There were multiple scars suggestive of trauma in the forehead. Systemic examination of the child was found to be grossly normal. The child underwent MRI of the brain which showed the presence of homogenously enhancing lesion in foramen of Monro extending into the frontal horn of the lateral ventricles, suggestive of Sub Ependymal Giant Cell Astrocytoma. Multiple areas of altered signal intensity in the cortical region of bilateral cerebral hemisphere were seen, suggestive of cortical tubers. Subependymal nodules and dilated left ventricles were also present. For further confirmation of diagnosis, ultasonography of kidney,

ureter and bladder(KUB) was performed which showed multiple hyperechoic lesions measuring 2-3mm located in cortex in bilateral kidneys, suggestive of Angiomyolipoma. Echocardiography of the child was also done to visualize any structural changes in the heart which was found to be grossly normal. Electeoencephalogram was also performed which showed a generalized, epileptiform discharge, spike and wave form <3 Hertz. There was no evidence of papilledema and hamartomas in bilateral eye of the child.

So, after accumulating all the findings a diagnosis of tuberculous sclerosis was made and the child was further managed accordingly.



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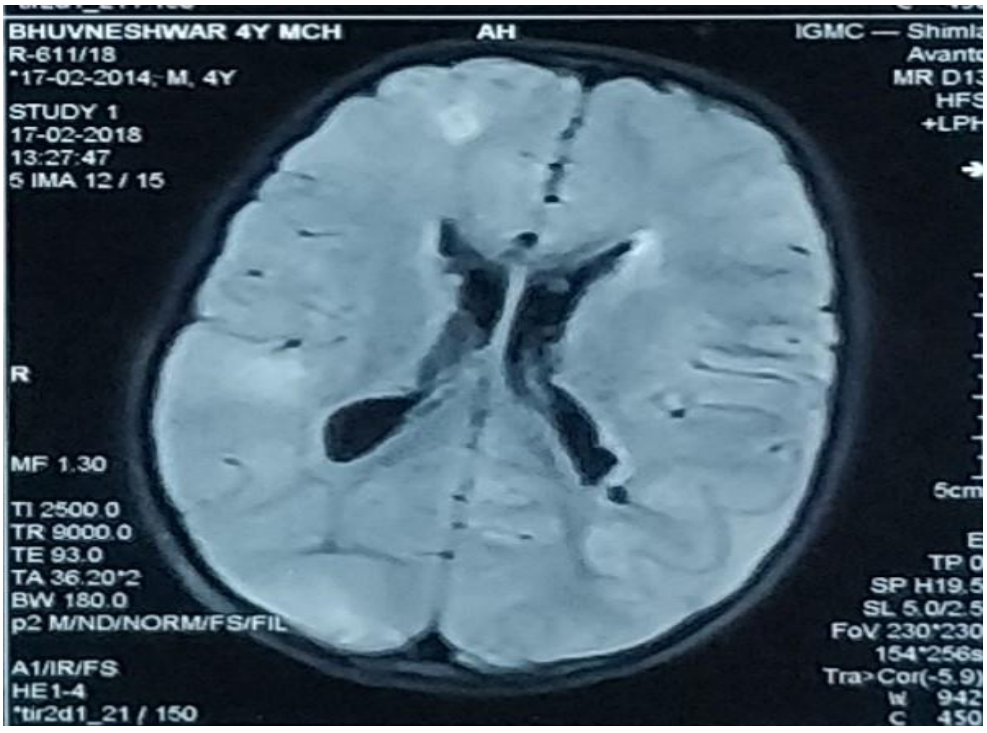
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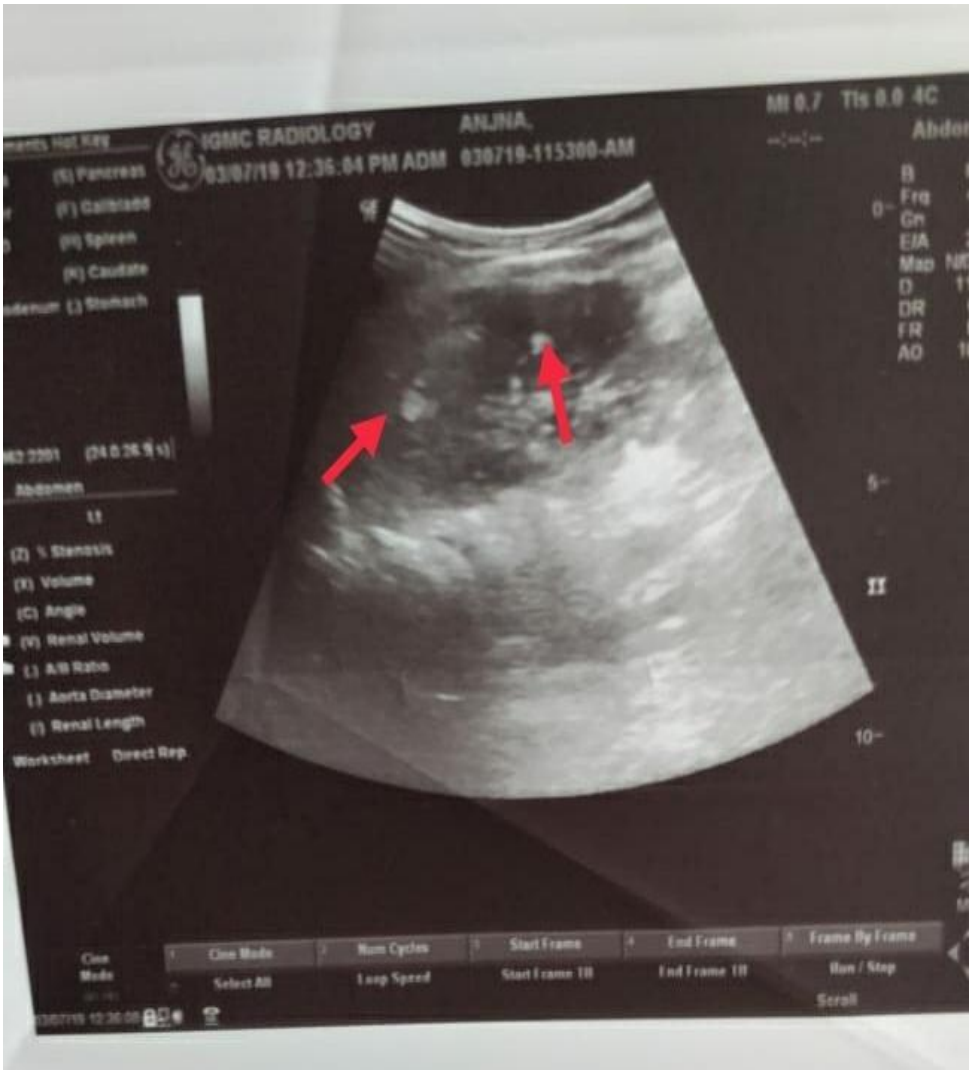

DISCUSSION

Tuberous sclerosis complex (TSC), also known as Bourne-ville disease or Bourneville -Pringle disease is a neurocutaneous syndrome (phakomatosis) inherited in an autosomal dominant manner and have a prevalence of 1 in 6000 newborns.[1]

The pathogenesis is said to be the mutation in TSC1 gene (9q34) which encodes for Hamartin protein or TSC2 gene(16p13) which encodes for Tuberin protein or both. The TSC1 and TSC2 genes are tumor-suppressor genes. The hamartin-tuberin complex is an important inhibitor of the mammalian target of rapamycin (mTOR). Its absence triggers loss of inhibition on cell proliferation and tumors growth.[5] The loss of either tuberin or hamartin protein results in the formation of numerous benign tumors (hamartomas).

TSC is a multisystem disorder with variable clinical manifestations. The wide spectrum of clinical features results from the formation of hamartomas in various organs. Hamartomas are frequently present in the skin, brain, kidneys, and heart and less frequently in lungs, retina, gingiva, bones, and gastrointestinal tract.[6]

Cutaneous manifestations are common and represent the most frequent findings in TSC.[7] These are typically the first clue to the diagnosis. The most prevalent of skin manifestations is the presence of hypomelanotic macules or "ash-leaf patches" occurring in 90–98% of cases. Skin hypopigmentation in the form of "confetti lesions" are seen on the anterior surface of the arms. Facial angiofibromas (adenoma sebaceum) are pathognomonic for TSC and are seen in over 70% cases. These are hamartomatous nodules of vascular and connective tissue, with a butterfly pattern over malar eminences and nasolabial folds of the face. Another common dermatological feature of TSC is the Shagreen patch which approximately occurs in 54% of patients. Ungual fibromas, also called Koenen tumors, are generally more common on toes than on fingers.[8]

Oral manifestations of TSC are characterized mainly by fibrous hyperplasia (angiofibromas) and dental enamel pitting.[9,10] Therefore, a detailed assessment of the oral cavity is crucial.

The most common neurological finding is seizures making epilepsy a significant cause of morbidity

associated with the disease. Features of autism and behavioural problems are frequently seen in these patients. Imaging techniques, especially MRI of the brain, are now well established for diagnosing and following up TSC patients. They are altered in 90 to 95% of cases[5], with the description of cortical tubers, subependymal glial nodules, white matter hamartomas, and subependymal giant cell astrocytoma. Cortical tubers are mostly supratentorial, in the frontal lobes.

Renal manifestations are the second most common findings after neurologic complications. The main manifestations are AMLs (80%) and cysts (17–47%). An association between TSC and renal malignancies has been recognized but is mostly anecdotal.

TSC is associated with both non retinal and retinal abnormalities. Non retinal abnormalities include eyelid angiofibromas, strabismus, cataracts, colobomas, and iris depigmentation. Hamartomas are the most common retinal manifestation present in about 40–50% of patients.[5]

Less common manifestations of TSC are cardiac rhabdomyoma, lung disease (lymphangioleiomyomatosis, multifocal micronodular pneumocyte hyperplasia, and clear cell "sugar" tumor), hepatic AMLs, splenic hamartomas, and also bony changes (sclerotic lesions).

The diagnosis of tuberous sclerosis is based on the clinical evidences with 7 major criteria present. The list of major and minor criteria for diagnosis of TSC is as follows:

Major	Minor
Cortical tuber	Cerebral white matter migration line
Subependymal nodule	Multiple dental pits
Subependymal Giant cell astrocytoma	Gingival fibromas
Facial angiofibroma	Bone cysts
Periungal fibroma	Retinal achromatic patch
Hypomelanotic macules	Confetti skin lesions
Shagreen patch	Nonrenal hamartomas
Multiple retinal hamartomas	Multiple renal cysts
Cardiac rhabdomyoma	Hamartomas rectal polyps
Renal angiomyolipoma	
Pulmonary lymphangioleiomyomatosis	

Definite TSC is a diagnosis when at least 2 major or one major plus 2 minor features are present. Possible TSC is a diagnosis when either 1 major or ≥2 minor features are present.

Since TSC is a systemic disease, a multidisciplinary approach is mandatory. Unfortunately the treatment is only supportive. Inhibitors of the mTOR pathway, such as rapamycin, also known as sirolimus, have an immunosuppressive and antiproliferative action. This drug is effective in reducing the volume of tumors in patients with TSC such as renal AMLs and subependymal giant cell astrocytoma.[11] Subependymal giant cell astrocytoma of size 2.1x1.8cm crossing midline with dilated ventricles is an indication for surgery and is a rare presentation of TSC.

Our patient had several findings such as subependymal giant cell astrocytoma, subependymal nodules, cortical tuber, renal angiomyolipoma and facial angiofibroma along with the history of seizure and cognitive deficit which led to the definitive diagnosis.

CONCLUSION

TSC is a genetic, autosomal dominant, multisystem involving neurocutaneous disorder that can cause variable expressions in the form of hamartomas in any organ. Recognition of specific radiologic features may help in early diagnosis and management and improve outcomes in TSC patients.

Conflict of interest
None.

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