CASE STUDY

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A case report on Tuberous Sclerosis

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ABSTRACT: Tuberous sclerosis complex is an autosomal dominant genetic syndrome that is characterized by a propensity for the occurrence of benign tumors preferentially in the skin, brain, and kidneys. Tuberous sclerosis complex is defined as a disorder of cell migration, proliferation, and differentiation. Although the exact mechanism that causes the uncontrolled proliferation of cells and the development of tumors is not known, it is generally accepted that these abnormalities in mTOR signaling contribute to the problem. It is thought that the proteins tuberin and hamartin regulate gene transcription and inhibit tumor growth. Usually, the first detected manifestations are infantile spasms, neurodevelopmental, and skin manifestations. Seizures, behavioral problems, and mental impairment are the main neurological symptoms of tuberous sclerosis. Treatment of acutely symptomatic subependymal giant cell astrocytomas is surgical resection. Asymptomatic subependymal giant cell astrocytomas may be treated with either surgical resection or therapy with mTOR inhibitors.

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INTRODUCTION:

Tuberous sclerosis (TSC) is a complex rare genetic disorder, which affects many organs, leading to benign tumors presenting preferentially in the skin, brain, and kidneys [1]. Mutations in the TSC1 or TSC2 gene are the underlying cause of TSC. Although it is inherited autosomally dominantly, the majority of cases are thought to result from apparent de novo mutations [2]. Pathologically, TSC is defined as a disorder of cell migration, proliferation, and differentiation [3]. TSC is characterized by the development of hamartias (non-growing lesions) and hamartomas which represent the primary instantiations of the complaint and affect colorful organ systems involving the central nervous system (CNS), dermatological (facial angiofibromas), feathers (renal angiomyolipoma), Circulatory (cardiac rhabdomyoma), eyes (retinal hamartomas) and

respiratory [4]. Usually, the first detected manifestations are infantile spasms, neurodevelopmental and skin manifestations also typically present early in life, on the other hand, renal manifestations are often observed in adolescence or adulthood and respiratory manifestations are typically present in adults and almost exclusively symptomatic in females TSC patients [5]. The dermatologic evaluation may aid in the early recognition of angiofibroma which may eventually cause cosmetic disfigurations, which may require laser therapy or surgical removal [6]. For renal angiomyolipomas larger than 3.5 cm, arterial embolization is recommended to avoid total nephrectomy and decrease the incidence of renal complications. Lesions measuring >3 cm, treatment with mTOR inhibitors is considered first-line therapy. For patients presenting with acutely bleeding renal angiomyolipoma, arterial embolization followed by corticosteroids is considered the treatment of choice [7]. Treatment of acutely symptomatic subependymal giant cell astrocytomas (SEGA) is surgical resection. Asymptomatic SEGA may be treated with either surgical resection or therapy with mTOR inhibitors [8]. The FDA has approved everolimus for TSC patients with symptomatic SEGA not amenable to surgery [9]. The aim of this case report is to highlight the symptoms of the condition and management according to individual patients.

CASE REPORT:

An 11-year-old male child was brought by her mother to the outpatient department (OPD) of a tertiary care hospital in Virudhunagar. The child presented with complaints of involuntary movements of both upper and lower limbs in the morning at around 9 a.m. with uprolling of eyeballs, fetal incontinence, and also with the involuntary passage of urine. The patient has had a known case of seizure disorder in the last 4 years of age and he is on antiepileptic drugs. Her mother reported that the child has had a history of colds and coughs for the past two days. The child was free from seizures for 24 hours. On the second day, the child's behaviour was very aggressive. On the fourth day of admission to the hospital, he developed a fever and was treated with paracetamol. On general examination, he was found to be awake, conscious, and afebrile. Physical signs included angiofibromas over the face. Other signs include neurocutaneous markers; brachycephaly is present; and green patches occur over the lower back region. He was slightly pale.

Laboratory Investigations showed Hb 10.2 gm/dL, WBC-9,100/cumm, Platelets 3, 75, 000 /cumm, RBC 3.92. Serum electrolytes Na^+: 132, K^+: 3.5, cl^-: 104. Routine urine examination was normal. Renal and liver function tests are normal.Echocardiographic examination was normal with LVEF – 60 %.

MRI SCAN BRAIN:

Observation:

- There is evidence of mild thinning of the corpus callosum noted with dilatation and splaying of lateral ventricles.
- Calcified tubers noticed with the ependymal lining of lateral ventricles foramen of Monro.
- There is evidence of subependymal giant cell astrocytoma (SEGA) noticed in the left frontal horn and forearm of Monro without obstructive hydrocephalus measuring 1.22 × 1.08 cm.
- Extensive cortical-subcortical periventricular and tubers with bifrontal parietal occipital cortical dysplasia.
- Branchicephaly with an increase in transverse diameter noted.
- Increase in AP diameter of both globes with thinning of both optic nerves seen.
- Brainstem and cerebellum appear normal.
- At present no obvious demonstrable angiomyolipoma of the kidneys is seen.

Impression:

The above findings are suggestive of tuberous sclerosis complex (TSC) with cortical-subcortical and ependymal periventricular tubers with bifrontal parietal occipital cortical dysplasia sub-ependymal giant cell astrocytoma (SEGA) in left frontal horn.

Table 1. Physical examination.

Parameters	Results		
CVS	S_1S_2 +		
RS	B/L AE +		
P/A	Soft		
CNS		Right	Left
	Tone – UL	Normal	Normal
	LL	Normal	Normal
	Power – UL	3/5	3/5
	LL	3/5	3/5

The patient has one younger brother who is unmarried. There is a family history of skin lesions over the face of his mother. His father has had a history of seizures. Other

family members did not have any skin lesions. On examination, the mother had angiofibroma over the face and neck region. Now the brother has started developing the same lesions over the neck and chest which were mild. Wood's lamp examination did not reveal any ash leaf spots. His father did not have angiofibroma or any other skin lesions.

The patient was treated symptomatically. Antipileptic drugs like T. Sodium valporate, and T. Trihexyphenidyl for controlling seizure episodes. T. Diazepam and T. Risperidone were given for behavioral changes.

DISCUSSION:

An autosomal dominant genetic syndrome known as tuberous sclerosis complex (TSC) is characterized by a propensity for the occurrence of benign tumors (hamartomas). It is brought on by changes in the hamartin and tuberin-encoding genes of TSC1 found on chromosome 9q34 and TSC2 found on chromosome 16p13.3 respectively [10]. A hereditary disorder called tuberous sclerosis can impact practically all organ systems. The pathophysiology involves changes to the TSC1 and TSC2 genes, which produce proteins that regulate the body's ability to generate new cells and multiply. Hamartomas may develop in the brain, skin, heart, kidney, liver, and lungs when this equilibrium is disrupted by gene alterations, impairing the functionality of these organs. Hamartin and tuberin are components of a complex that regulates the body's cell division and growth. Although the exact mechanism that causes the uncontrolled proliferation of cells and the development of tumors is not known, it is generally accepted that these abnormalities in mTOR signaling contribute to the problem. It is thought that the proteins tuberin and hamartin regulate gene transcription and inhibit tumor growth [11]. Though other characteristics may help with the diagnosis, cutaneous symptoms are typically the first indication that a patient has TSC. In 75 % of patients, facial angiofibroma is present. These lesions may be mistaken for acne when they first emerge after age 5 years. The earliest skin lesion in TSC patients is the ash-leaf spot. By the age of 4 years, 90 to 96 % of patients may develop ash leaf marks. Seizures, behavioral problems, and mental impairment are the main neurological symptoms of TSC [12].

CONCLUSION:

Our case presented with major features like facial angiofibroma, behavioral changes, and subependymal nodules. Combining his past clinical history of seizures, the cutaneous manifestations, and the imaging findings, a definitive diagnosis of the Tuberous sclerosis complex was made. Although there is no known cure, there are only symptomatic treatments available.

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