

## A CASE REPORT OF FAMILY OF TUBEROUS SCLEROSIS WITH INCREASING NEUROLOGICAL MANIFESTATION WITH EACH GENERATION

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### ABSTRACT

Tuberous sclerosis is an autosomal dominant disease affecting every generation of the family with widespread manifestation from skin, central nervous system, kidney, heart, etc. Tuberous sclerosis is an extremely heterogeneous disease with wide clinical spectrum varying from severe mental retardation and incapacitating seizures to normal intelligence and lack of seizures, often within the same family. As a general rule, the younger the patient presents with symptoms and signs of Tuberous sclerosis, the greater the likelihood of mental retardation. We here have a case report of a family of tuberous sclerosis with increasing number of cortical tubers and neurological manifestation with each generation of the family.

### KEYWORDS

Tuberous Sclerosis, Adenoma Sebaceum, Angiofibroma, Seizures, Mental Retardation, Cortical Tubers.

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**CASE REPORT:** A 13-year-old girl presented to the medical emergency with recurrent seizures. Patient had history of recurrent tonic seizures of one day duration associated with frothing of mouth, uprolling of eyes. No h/o spontaneous passing of urine and faeces with postictal confusion, not responding to the routine medications at presentation. There was no h/o fever, no h/o weakness of limbs and face, no h/o visual disturbances, no h/o abdomen pain, no h/o haematuria, no h/o syncope, no h/o chest pain, no h/o abdominal distension. On detailed history from the parents, they revealed that this was the first episode of seizure for the patient and the girl had autistic behaviour, shyness, was an introvert, stopped schooling due to her poor academic performance and concentration lapses. Ongoing further into the detailed family history, mother revealed that the girl's younger brother also had early onset of seizure episodes from five years of age and was on medication since then. He exhibited hyperactive behavioural pattern with attention deficits. He also suffered from poor academic performance as his intelligent quotient was low. He also had the same cutaneous lesions on his face like his mother and sister. Also the girl's grandmother also had similar facial cutaneous lesions.

On general examination, patient was conscious, afebrile and there was no significant pallor, icterus, cyanosis or clubbing. No evidence of pedal oedema or generalised lymphadenopathy. Cutaneous examination revealed

adenoma sebaceum (fig. 1, 3), ash leaf macules (fig. 2), Shagreen patches (fig. 2), periungual swelling.

**CNS EXAMINATION:** Patient was irritable, was able to communicate adequately, oriented to place and person, Examination of the Cranial nerves, Spino-motor systems and Sensory components did not reveal any significant abnormality. Ophthalmic examination revealed no significant abnormality with normal fundus. Examination of the Cardiovascular and Respiratory systems also showed no significant abnormality. There was no abdominal mass or fluid collection in the abdominal examination.

The boy also had various cutaneous markers as his sister as described earlier.

IQ testing of the girl showed mild mental retardation (60%) with attention deficits.

IQ testing of the boy showed moderate mental retardation (45%) with significant attention deficits in dual tasks and divided attention, utilising TEST OF EVERYDAY ATTENTION FOR CHILDREN (TEA-ch.). IQ testing of the mother showed normal intelligence with mild attention deficit in dual task performance.

On investigation, haemogram and other routine investigations were within normal range.

Chest x-ray & ECG for both the children showed no significant abnormalities.

CT brain of the girl showed bilateral calcified subependymal nodules. MRI showed subependymal tubers and bifrontal focal cortical tubers and signal void in the gradient sequences suggestive of calcified tubers, whereas CT brain of the boy also showed bilateral subependymal calcific nodules (fig. 4).

MRI showed multiple hyperintense foci in both the frontal (fig. 5) and temporal regions suggestive of cortical

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tubers (fig. 6). MR image also demonstrated superficial white matter abnormalities and subependymal tubers.

EEG showed hypsarrhythmic patterns in both the children.

Ultrasound abdomen showed no significant abnormalities.

So based on the clinical, radiological, familial history, the diagnosis of tuberous sclerosis was made and the patients were started with Tab phenytoin and Tab sodium valproate on recommended dosages. Patients were referred for both psychiatric and behavioural therapy after which both the girl and boy showed improvement in cognitive behaviour and control of seizures.



**Fig. 1: Adenoma Sebaceum**



**Fig. 2: Ash leaf Macule & Shagreen Patch**



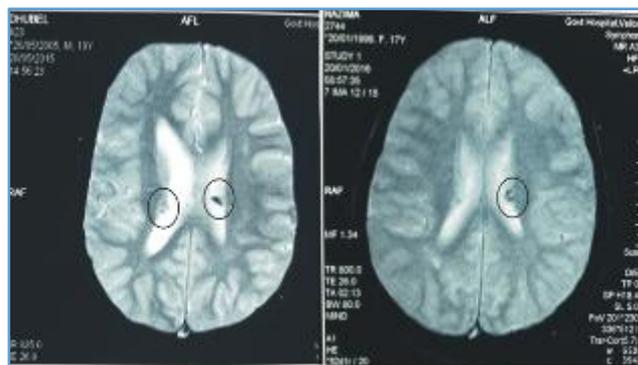
**Fig. 3: Facial Angiofibromas, Gingival Angiofibromas**



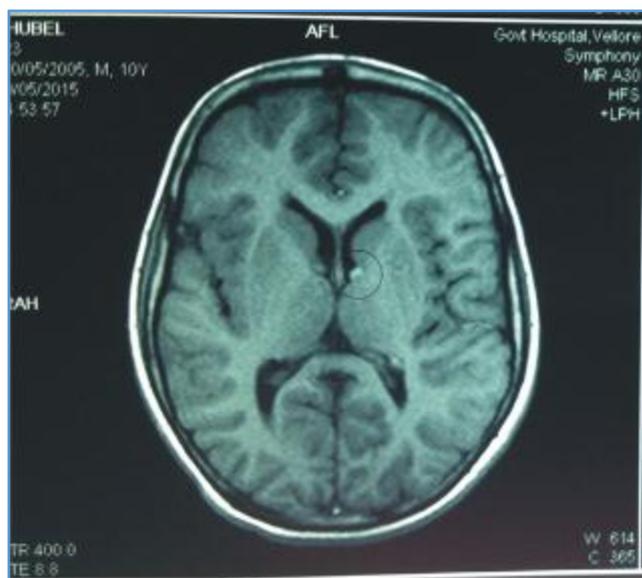
**Fig. 4: CT Brain Showing Subependymal Calcified Nodules**



**Fig. 5: MRI Brain showing Focal Cortical Tubers in both Frontal Lobes**



**Fig. 6: MRI Brain Showing Cortical Tubers**



**Fig. 7: MRI Brain Showing Subependymal Tubers.**

#### DISCUSSION:

- This is an autosomal dominant disorder with an incidence of approximately 1 in 5000-10000 live births. It is caused by mutations in either the TSC1 gene in chr.9q34 which encodes a protein termed hamartin or the TSC2 gene, which maps to chr.16p13.3 and encodes the protein tuberin. Hamartin forms a complex with tuberin, which inhibits cellular signalling through the mTOR and acts as a negative regulator of the cell cycle.
- Patients with tuberous sclerosis may have seizures, mental retardation, adenoma sebaceum, Shagreen patches, hypomelanotic macules, periungual fibromas, renal angiomyolipomas and cardiac rhabdomyomas. These patients have an increased incidence of subependymal nodules, cortical tubers and subependymal giant-cell astrocytomas (SEGA).
- Patients frequently require anticonvulsants for control of seizures.
- SEGAs do not always require therapeutic intervention, but the most effective therapy is with the mTOR inhibitors sirolimus or everolimus which often decrease seizures as well as SEGA size.
- A number of meta-analyses demonstrate that MRI detected cortical tubers is six times more likely to be above the median count for tuberous sclerosis patients with severe cerebral dysfunction (poor seizure control/moderate-to-severe retardation, than more mildly affected tuberous sclerosis. Similarly, various studies showed moderate-to-severely affected person are five times more likely to have greater than seven MRI detected cortical tubers than mildly affected patients. Cortical tubers of tuberous sclerosis form in early gestational period, the embryological disruption determining the clinical severity of cortical dysfunction of tuberous sclerosis is set in the early gestational period.<sup>1</sup>

Tubers localised to the inferior parietal lobes, middle frontal lobes, middle temporal lobes, or central sulcus regions were associated with a high frequency of epileptogenic tubers. Epileptogenic tubers occurred statistically more frequently within the inferior parietal lobe and within the central sulcus region in children younger than 1 or between 1 and 3 years old respectively.<sup>2</sup>

Failure to detect focal cortical dysplasia and similar lesions encountered in patients with tuberous sclerosis can have significant clinical consequences. So the beneficial effects on detection of FCD and cortical tubers when using a magnetisation transfer T1 sequence for children with seizures who underwent MRI has been studied.<sup>3</sup>

Although patients with a TSC1 mutation are more likely to have a less severe neurologic and cognitive phenotype than those with a TSC2 mutation, the considerable overlap between both aspects of the phenotype implies that prediction of the neurologic and cognitive phenotypes in individuals with tuberous sclerosis complex should not be based on their particular TSC1 or TSC2 mutation.<sup>4</sup> The diagnosis of tuberous sclerosis complex in infancy is aided by a high index of suspicion and timely access to neuroimaging. Early diagnosis of tuberous sclerosis complex may be essential to the success of future therapies by providing a window of opportunity.<sup>5</sup>

Epilepsy is very common in tuberous sclerosis complex and occurs in 80 to 90% of affected individuals during their lifetime. Onset usually occurs during childhood, and up to one third of children with tuberous sclerosis complex will develop infantile spasms. Although not completely understood, the incidence of epilepsy is thought to relate to the neuropathologic features of the disorder, including cortical tubers and other dysgenetic features. Individuals with tuberous sclerosis complex frequently have epileptiform features to their electroencephalograms. Treatment of epilepsy in tuberous sclerosis complex is similar to epilepsy resulting from other causes and includes anticonvulsant medications, the vagus nerve stimulator and ketogenic diet. Vigabatrin has been shown to be particularly effective in treating infantile spasms in the setting of tuberous sclerosis complex. Epilepsy surgery has a very important role in the management of children and adults with Pharmaco-resistant epilepsy in tuberous sclerosis complex.<sup>6</sup>

In relation to seizure control, the specificity of an abnormal sleep EEG and the positive predictive value of normal sleep EEG were 100%. MRI and EEG background were neither sensitive nor specific for predicting seizure control. A majority of children with tuberous sclerosis complex can achieve good seizure control. The sleep EEG is helpful in predicting eventual seizure control.<sup>7</sup>

**CONCLUSION:** This case reports the highlights of the increasing neurologic manifestations with each passing generation in families affected with tuberous sclerosis complex in terms of seizure activity, the number of tubers in MRI imaging and intelligence. As earlier studies suggested, in our case report also, the increased number of cortical tubers in each generation presented with increased seizure

episodes with poor control, delayed milestones and poor scholastic performances.

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