Case Report

A Rare Case of Tuberous Sclerosis with Giant Cell Astrocytoma

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Author's Contribution

[1] Conception of study
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Abstract

Tuberous sclerosis complex (TSC) is a neurocutaneous disease inherited in an autosomal dominant pattern with variable penetration. This case report is of a 12-year-old boy who presented with complaints of headache, vomiting, and fits. His neurocutaneous stigmata combined with radiological imaging led us to the diagnosis of TSC with sub-ependymal giant cell astrocytoma (SEGA). His family screening revealed interesting details of how the disease is running in his family. He is now scheduled for surgery at our neurosurgery department for the removal of SEGA.

This case is significant because it is a typical depiction of the classic pattern of autosomal dominant inheritance of TSC with evident variable penetration within members of the same family.

Introduction

Tuberous Sclerosis Complex (TSC) is a relatively rare but important neurocutaneous syndrome. It is a multisystem heterogeneous disease that is characterized by the formation of multiple benign tumors called hamartomas in various organs of the body. In the brain, these occur in the form of cortical and subcortical tubers, subependymal nodules, and subependymal giant cell astrocytomas (SEGAs). Other organs involved in different degrees include kidneys, skin, heart, eyes, and lungs. Disease manifestations can occur at any age, with no set clinical presentation.[1] High index of suspicion often leads to the diagnosis.

Case Report

A 12-year-old boy was brought by his parents with complaints of headache, vomiting for one and a half months; and two episodes of generalized tonic fits. He was otherwise a developmentally normal child, a product of non-consanguineous marriage with unremarkable history. He had one elder brother who was a known epileptic on anticonvulsant medications with poorly controlled fits. He had one accompanying EEG which showed intermittent delta waves in bilateral parieto-occipital regions. On examination, he was vitally stable with BP within normal centiles. He had nodulopapular rash on his face (facial angiofibromas) and three hypomelanotic spots on his body. The rest of his general physical, systemic, and CNS examination was unremarkable. His fundoscopic examination revealed bilateral papilledema.

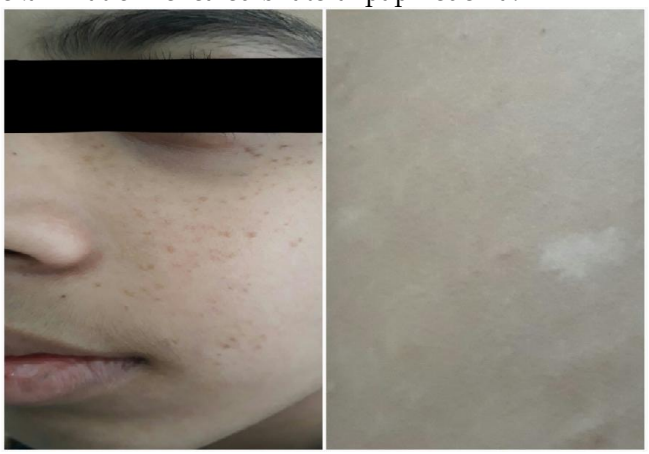

Figure 1: (A) Facial angiofibromas.
(B) Hypomelanotic macules of the index case

He was admitted with initial suspicion of a space-occupying lesion. CT scan, followed by MRI showed Subependymal giant cell astrocytoma, subependymal calcifications, and cortical tubers with the tumour being just adjacent to Foramen of Monro and causing obstructive hydrocephalus; thus radiologically confirming Tuberous Sclerosis with giant cell astrocytoma. His echocardiography, retinal examination for hamartomas, renal ultrasonography, and chest X-ray, all performed for associated features of TSC were normal. Thus 5 the major diagnostic criteria of TSC were fulfilled in the patient. (Figure 2, Figure 3)

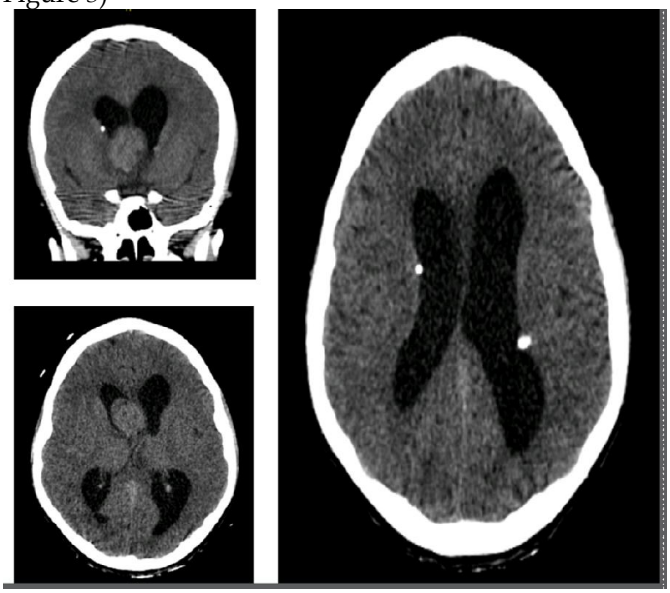

Figure 2 (A) CT Scan image showing giant cell astrocytoma and a single subependymal calcification.
(B) An axial view of Giant cell astrocytoma.
(C) Two subependymal calcifications in an axial view.

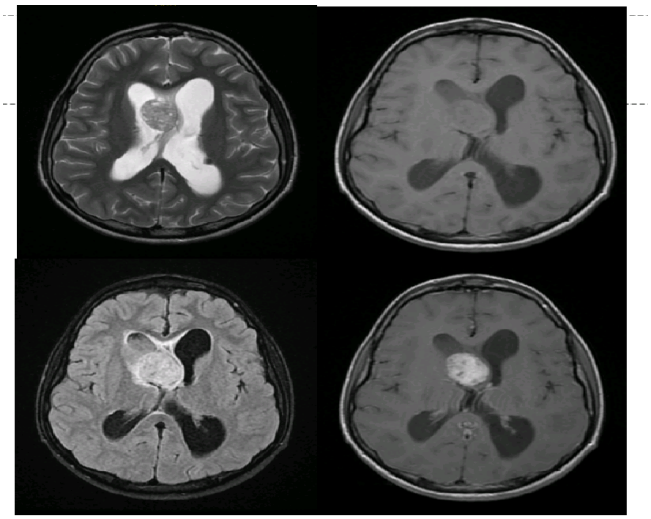

Figure 4: MRI of the index case with a clear view of giant cell astrocytoma near the right Foramen of Monro. It appears hyperintense on T1WI

heterogeneously hyperintense on T2WI, and hyperintense on FLAIR sequence; with heterogenous post-contrast enhancement

His family was then screened and on examination, his elder brother, who was already an epileptic, also had facial angiofibromas and multiple hypomelanotic macules, fulfilling two of the major criteria for TSC. Radiological features of TSC were absent. The patient's mother also had facial angiofibromas but no other clinical features of TSC.

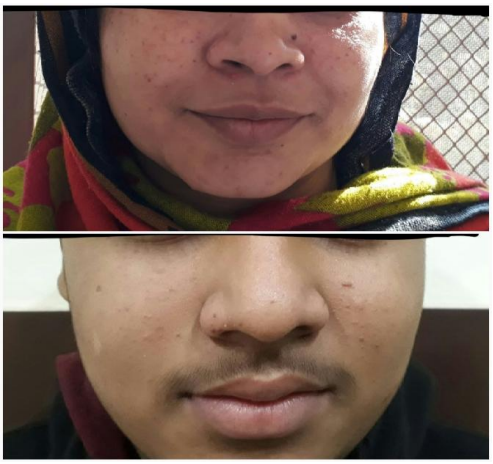

Figure 5: (A) Facial angiofibromas in index case's mother.
(B) Facial angiofibromas in index cases brother.

He was medically managed with oral sodium valproate, and since his SEGA was symptomatic and warranted surgical intervention, neurosurgical consultation was sought. The child was then shifted to the neurosurgical department for surgery.

Discussion

The name Tuberous Sclerosis is derived from the Latin word tuber (root-shaped growths) and the Greek word skleros (hard), referring to thick, firm 'tubers' found in the brains of patients with TSC. It was first described by Desire-Magloire Bourneville in 1880.[2] Scarce literature estimating the incidence of TSC has been published in the last decade, but older studies estimate the birth incidence to be 1 in 6000 newborns.[3]
TSC is an autosomal dominant disorder with variable penetrance. It is caused by heterozygous mutations in either *TSC1* or *TSC2*. TSC1 and TSC2 genes encode *hamartin* and *tuberin* proteins respectively. These two proteins bind and work together in a cell. Thus the loss of either results in the non-functioning of the other. Both TSC1 and 2 are tumour suppressor genes, and their loss of function is what results in the formation of the TSC characteristic benign tumours which are named hamartomas. There are more than 1,500 known pathogenic variants for *TSC1* and *TSC2*, leading to loss of function effects on TSC1 and TSC2. [(4)] Mutations in either *TSC1* or *TSC2* result in hyperactivation of the mTOR gene, which in turn results in accelerated nucleotide and protein synthesis resulting in increased cell growth but with decreased autophagy.[5]
Clinical manifestations vary widely among individuals suffering from TSC; as well as amongst members of the same family inheriting the same gene mutation. Moreover, spectra of disease manifestations change and evolve during the lifetime of the patient.[1] Therefore, TSC is diagnosed based on a set diagnostic criterion, which encompasses some major and some minor components. The diagnostic criterion considers both clinical and radiological findings. The presence of two or more major or one major and two or more minor criteria confirm the diagnosis.[6] (Table 1 and Table 2)

Table 1:

Major Criteria
Cortical Tubers
Subependymal nodules
Subependymal giant cell astrocytoma
Facial angiofibroma or forehead plaque
Ungal or periungal fibromas
Hypomelanotic macules (>3)
Shagreen patch
Multiple renal hamartomas
Cardiac rhabdomyoma
Renal angiomyolipoma
Pulmonary lymphangioleiomyomatosis

Table 2:

Minor Criteria
Cerebral white matter migration lines
Multiple dental pits
Gingival fibromas
Bone cysts
Retinal achromatic patch
Confetti skin lesions
Non-renal hamartomas
Multiple renal cysts
Hamartomatous rectal polyps

The hallmark of TSC is central nervous system involvement. The most common neurological

manifestations consist of epilepsy, cognitive impairment, and psychiatric or autism spectrum disorders. Next commonly involved systems include the dermatological and renal systems.[7] Infants may present with infantile spasms with a hyps-arrhythmic EEG pattern; often followed by virtually any other seizure type, leading to refractory epilepsy in up to 75% of cases.[8]

Once diagnosed, the patient should be screened for all the associated features. The family of the index case should also be screened. Patients should be kept on long-term follow-up and a multidisciplinary approach should be used. Follow-up screening included brain MRI and renal imaging every 1-3 years. Complications should be dealt with as encountered.

Rapamycin has a proven role in facial angiofibromas and hypomelanotic macules.[9,10] Everolimus is an FDA-approved drug with proven efficacy for both asymptomatic sub-ependymal giant cell astrocytomas (SEGAs), as well as renal angiomyolipomas.[11] Everolimus is also gaining popularity for the treatment of multi-drug-refractory epilepsy.[12] Symptomatic SEGAs require neurosurgical intervention.

Renal lesions are the main cause of death among patients with TSC and warrant vigilant surveillance. Other causes include sudden death due to epilepsy and pulmonary lesions.[13]

Prenatal screening should be offered to all expectant mothers suffering from or having a family history of TSC. Fetal echocardiography for cardiac rhabdomyomas, and targeted genomic sequencing are the possible options.[14]

Conclusion

- A pediatrician should have a keen eye for any unusual skin spots or lesions to not let any neurocutaneous stigmata unnoticed.
- On diagnosing a patient with TSC, the index case's family must be screened keeping in mind varying clinical presentations of the disease.
- Each diagnosed case must be followed up yearly for disease progression and for performing screening MRI.

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