Surgical Management of Tuberous Sclerosis

SHEIKH MUHAMMAD AFZAL, MUHAMMAD ANWAR*, SALAH-UD-DIN ARBI
Naseer Ahmad Ch.
Department of Neurosurgery, Sheikh Zayed Hospital, Rahim Yar Khan
**Department of Neurosurgery, PGMI / Lahore General Hospital, Lahore*

ABSTRACT

Tuberous sclerosis is a genetic disorder with incidence of 1 into 6000 birth. It is a multi-systemic disorder. Seizures associated with tuberous sclerosis (TS) can be difficult to control with medical therapy.

Objective: *To determine the role of surgery for the management of seizures and other symptoms in Tuberous Sclerosis.*

Material and Method: *Four patients with TSC who underwent surgery were admitted in the Department of Neurosurgery Sheikh Zayed Hospital, Rahim Yar Khan and Department of Neurosurgery, PGMI / Lahore General Hospital, Lahore.*

Results: *We admitted 5 cases, 3 males and 2 females. All presenters with seizers other presenting feature were headache and vomiting in all 5 cases, vomiting in 5 cases. All cases were operated were craniotomy and removal of tumour. Surgery were V.P. Shunt was performed in 3 cases. All 5 cases revealed excellent outcome and seizures well controlled with anticonvulsant postoperatively which were poorly controlled preoperatively. All 5 cases were discharged in satisfactory condition within 2 – 3 weeks. Histopathology the histopathology of all 5 cases were subependymal giant cell astrocytoma (SEGA).*

Outcome: *All 5 cases revealed excellent outcome and the seizures were well controlled post-operatively with anticonvulsants. While pre-operative fits, were poorly controlled. All 5 cases were discharged in satisfactory condition with 2 – 3 weeks.*

Conclusion: *The surgery had excellent outcome for tuberous sclerosis provided timely decision is taken to treat the tumor and associated hydrocephalus. Most of these patients will lead ventriculoperitoneal shunt or EVD as an emergency step to save the life.*

Key Words: *Epilepsy, Tuberous Sclerosis.*

Abbreviations: *TCS: Tuberous Sclerosis, EVD: External Ventricular Drain, VP Shunt: Ventriculoperitoneal, SEGA: Sub-ependymal Giant Cell Astrocytoma.*

INTRODUCTION

It is rare multi-systemic genetic disease that cause non-malignant tumor to grow in the brain and other vital organs such as the kidney, heart, eyes, lungs and skin.

The name, composed of the Latin **tuber** (Swelling) and the Greek **Sclerosis** (hard). It refers to the pathological finding of **thick, firm pale gyri** called "tubers" in the brain of patient's postmortem. The tubers were first described by Desire Magloire Bourneville in 1880; the cortical manifestation may sometimes still be known by the eponym Bourneville disease.

Unifocal onset seizures and mild to no development delay at the time of surgery are predictive of excellent long term outcome. Tubers and sub ependymal nodules (SENs) are the typical brain lesions in TCS, and are present in 90 – 95% of the patients.

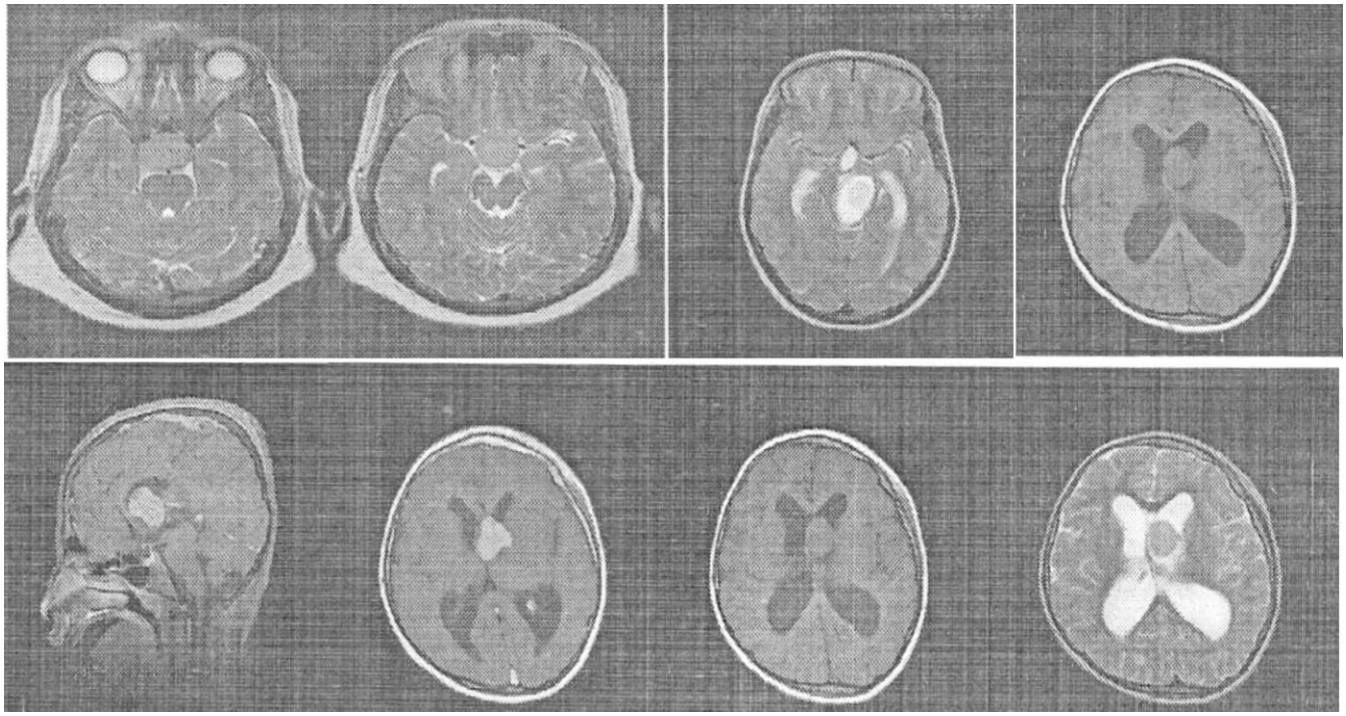

Fig. 1: *Pre-operative MRI showing Periventricular Tumour Extending into the Ventricle.*

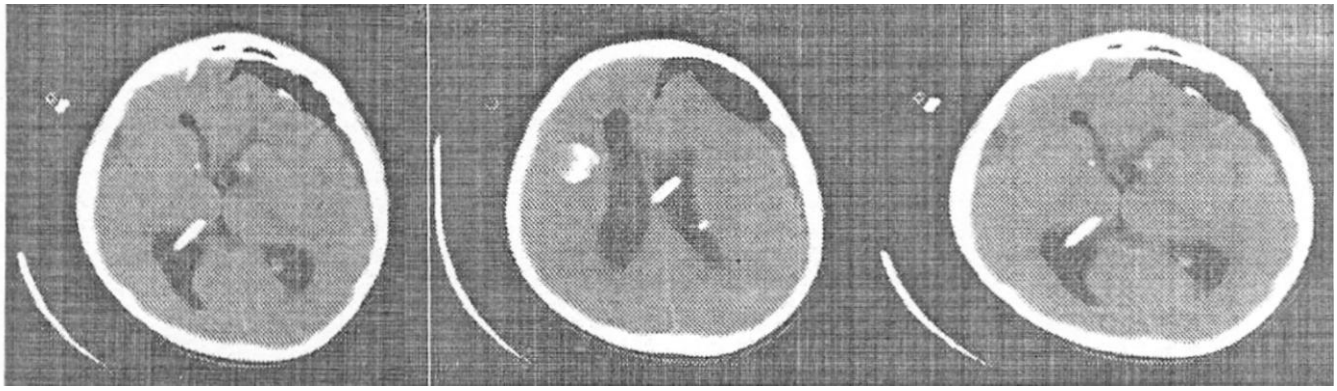

Fig. 2: *Post-operative CT Scan Brain showing Gross Total Removal of Tumor and VP Shunt in Situ.*

Three types of brain tumors may be associated with TSC.

1. **Giant cell astrocytoma** (grows and block the CSF flow).
2. **Cortical tubers.**
3. **Sub-ependymal nodules;** form in the wall of ventricles.

1. These nodules have a tendency to **calcify** as the patient ages. A **nodule** that marked by enhancement and enlarges over time, leads to transformation into **Sub-ependymal giant cell astrocytoma (SEGA)**.

A SEGA typically develops in the region of foramen of Monro leading to obstructive hydrocephalus.

In infants, the first clue is often the presence of seizures, delayed development or white patches on the skin.

MATERIAL AND METHOD

This is a retrospective and prospective study and conducted at Department of Neurosurgery, Sheikh Zayed Hospital, Rahim Yar Khan and PGMI / LGH, Lahore. Mode of admission was through OPD and

Table 1: *The diagnosed criteria consists of major and minor diagnostic criteria.*

Major Features				
	Location	**Sign**	**Onset**	**Note**
1.	Head	Facial angiofibromas or forehead plaque	Infant – adult	
2.	Fingers and toes	Non-traumatic ungula or perifungual fibroma	Adolescent – adult	
3.	Skin	Hypomelanotic macules	Infant – child	More than three
4.	Skin	Shagreen patch (connective tissue nevus)	Child	
5.	Brain	Cortical tuber	Fetus	
6.	Brain	Sub-ependymal nodule	Child – adolescent	
7.	Brain	Sub-ependymal giant cell astrocytoma	Child – adolescent	
8.	Eyes	Multiple retinal nodular hamartomas	Infant	
9.	Heart	Cardiac rhabdomyoma	Fetus	Single or multiple
10.	Lungs	Lymphangioleiomyomatosis	Adolescent – adult	
11.	Kidneys	Renal angiomyolipoma	Child – adult	10 and 11 together count as one major feature
Minor Features				
	Location	**Sign**	**Onset**	
12.	Teeth	Multiple randomly distributed pits in dental enamel		
13.	Rectum	Hamartomatous rectal polyps	Histological confirmation is suggested	
14.	Bones	Bone cysts		
15.	Brain	Cerebral white – matter “migration tracts”	Radiographic confirmation is sufficient. 5 and 15 together count as one major feature	
16.	Gums	Gingival fibromas		
17.	Liver, spleen and other	Non-renal haemartoma	Histological confirmation suggested	
18.	Eyes	Retinal a chromic patch		

Emergency and we admitted we included 5 cases in our study, age varies from 9 to 22 years. Duration of study was 5 years from Jan. 2009 to Jan. 2013. Mean follow-up period of 2 years. The detail of 5 cases is below:

1st Case

The first patient 22 years females came with H/O headache and seizure from last six months. She has generalized developmental delay which affects her school performance. She was getting phenytoin 100 mg TID table. MRI brain plain and with contrast was done which showed periventricular tumor and a small lateral ventricular hemorrhage.

On examination, there was no cutaneous manifesttation.

She was prepared for surgery. After a taking all the measures, surgery was done under G/A i.e. Right frontal craniotomy was done.

The approach was interhemispheric transcallosal and lateral ventricular tumor was removed. Biopsy confirmed to be sub-ependymal giant cell astrocytoma.

She continued to get phenytoin 100 mg TID. Later on, she developed hydrocephalus and finally VP shunt was done. She was discharged from ICU after a few days with satisfactory condition, confirming be the case of tuberous sclerosis, histopathologically.

2nd Case

The Second case 12 years old boy known case of seizure since 4th day after birth, remained admitted in ICU for one month and he was getting antiepileptic drug for seizure disorder since birth.

He came with H/O Headache, vomiting and seizure disorder again. CT scan brain done which shows intra-ventricular tumor with hydrocephalus, Sub-ependymal nodules and cortical tubers. USG of abdomen shows Cystic lesions in the renal parenchyma. Patient was having aggressive behavior, agitation, Headache and vomiting.

Immediately, patient was advised for VP shunt and VP was done after the completion of all requirements.

After one week, patient was prepared for main surgery and left frontal craniotomy was done and intra-ventricular tumor resection was done through trans-cortical approach.

Biopsy confirmed to be subependymal giant cell astrocytoma.

After two weeks stay in hospital patient was discharged with anti-epileptic drugs in satisfactory conditions.

3rd Case

3rd was 9 years male who was hyperactive, inattentive, impulsive and distractible. He speaks full sentence with reasonable articulation socially immature and has some obsessional feature. He came for seizure and headache at occipital region. Patient has also cutaneous stigma.

MRI of brain shows intra-ventricular tumor; suggestive of tuberous sclerosis.

He was prepared for surgery and right frontal craniotomy done with gross total resection of tumor done and EVD was inserted in ventricle for one week. Biopsy of tissue was sub-ependymal giant cell astrocytoma.

4th Case

Fourth patient was two years female child came H/O seizure, intractable with conservative management. On examination, there were shagreen patches on her skin particularly back.

MRI of brain was advised. It showed sub-ependymal growth in lateral ventricle and tubers scattered all over the brain. There was moderate Hydrocephalus. In emergency, EVD was done. In the next day patient was prepared for surgery and the Left frontal craniotomy done and sub-ependymal growth was removed. Biopsy confirmed the sub-ependymal giant cell astrocytoma (SEGA). It was typically near the region of foramen of Monro.

Later on, in next week, VP shunt was done. After one week, she was discharged on anticonvulsant drugs with satisfactory remarks.

5th Case

Fifth case was main, 30 with age, presenting with headache, vomiting and seizures. CT / MRI revealed left paraventricular tumour compressing the lateral ventricular. He was operated by craniotomy left parietal region and grass total removal of tumour was performed. Patient has good recovery and was discharged within one week in satisfactory conditions. Histopathology report was subependymal giant cell astrocytoma (SEGA).

Diagnostic Criteria

Table 1 shows the detail of diagnostic criteria. The selection for cases for tuberous sclerosis was based on the following criteria.

Inclusion Criteria

1. Seizure of various kinds. The occurrence of infantile spasm has been contrasted with other types of seizures.
2. Delayed milestones with hyperactive, inattentive, impulsive and distractible attitude.
3. Non-pigmented or hypo-pigmented areas of the skin of limb or trunk.
4. Other manifestation such as lesion of the kidney viz renal angiomyolipoma.

RESULTS

Sex Incidence

There were 3 male and 2 females as shown in table 2.

Table 2: *Sex Incidence.*

Sex	Number	Percentage
Male	3	60%
Female	2	40%
Total	5	100%

Age Range

Age range was 9 to 32 years.

Clinical Feature

Table 3 shows the clinical feature. The age at which mental defect (1 Q? 70), poorly pigmented areas of skin along with lesion in kidney was noted. In one patient shagreen patches in lower half of trunk in back were noted.

Table 3: *Clinical Presentation.*

Clinical Presentation	Number	Percentage
Seizures	5	100%
Headache	5	100%
Vomiting	5	100%
Aggressive Behaviour	3	60%
Developmental Abnormalities	3	60%
Poor Pigmentation of Skin	3	60%
Shagreen Patches Skin	1	20%
X-ray Intracranial Calcification	2	40%
Other Organs Involvement Like Kidney	1	20%
Tubers in Brain	4	80%

Seizures, headache and vomiting were presenting symptoms in all 5 (100%) cases, Aggressive behavioural in 3 (60%) cases, Developmental abnormalities in 3 (60%), Poor pigmentation in 3 (60%) cases were other important symptoms, Shagreen patches on Skin in 1 (20%) case. Plain x-ray skull revealed intracranial calcification in 2 (40%) cases.

Surgical Procedure

Table 4 shows the detail of surgical procedure. Frontal craniotomy and Trans-cortical approach for lateral ventricular tumor was adopted 3 (20%) cases and Frontal Inter-hemispheric, transcallosal approach was used 1 (20%) case. Temporoparietal Craniotomy was done 1 (20%) case.

Table 4: *Surgical Procedure.*

Cases	Procedure 1	Procedure 2	Procedure 3
1	Right Frontal Craniotomy and Interhemispheric Transcallosal Approach for Intraventricular Tumour	V. P. Shunt	
2	V. P. Shunt	Left Frontal Craniotomy, Trans-cortical Approach for Paraventricular Tumour	
3	Right Frontal Craniotomy, Trans-cortical Approach for Intraventricular Tumour	EVD for One Week	
4	EVD	Left Frontal Craniotomy Trans-cortical Approach for Intraventricular Tumor	V. P. Shunt
5	Left Temporoparietal Craniotomy and Trans-cortical Approach		

Table 5: *Histopathology.*

Histopathology	No. of Cases	Percentage
Sub-opendymal Giant all Astrocytoma (SEGA)	5	100

Histopathology

Table 5 shows the detail of histopathology. The histo-

pathology of all 5 cases were subependymal giant cell astrocytoma (SEGA).

OUTCOME

All 5 cases revealed excellent outcome and the seizures were well controlled post-operatively with anticonvulsants. While pre-operatively was, fits were poor controlled. All 5 cases were discharged in satisfactory condition with 2 – 3 weeks.

DISCUSSION

The tuberous sclerosis (TSC) complex, a multisystem, autosomal dominant disorder, affecting children and adults, results from mutation in one of two genes. It was first described by Bourneville in 1880, causes disabling neurological disorders; epilepsy, mental retardation and autism. In some patients, there may be hypo-pigmented skin patches, facial angiofibroma, renal angiomyolipomas and pulmonary lymphangiomyomatosis.

In our 5 cases, 4 cases presented in emergency department with seizures, on further radiological finding, one has renal cystic lesion. In MRI and CT, 4 (80%) patients showed tuber in brain and 4 patients had sub-ependymal ventricular growth. In 1 patient there were skin pigmentation i.e. on the back and lower trunk, shagreen patches was observed.

In spite of wide variety of clinical presentation in TSC some form of seizure occurred in 100% of our patients, but in literature infantile spasm were an early type of seizure in 69% of children.

The TSC_1 – TSC_2 complex plays a central role in the integration of multiple cues to regulate cellular growth and differentiation. Mutations in TSC_1 or TSC_2 result in widespread, devastating consequences. Key priorities for future research include elucidating the location of and functional relationship between TSC_1 and TSC_2 and their pathways, determining whether Rheb is the sole downstream effect or of the TSC_1 – TSC_2 complex and whether mTOR is the only clinically relevant target of Rheb, understanding the relationship between tubers and epilepsy, and investigating the role of estrogen in the pathogenesis of lymphangiomyomatosis. The recent delineation of the TSC biochemical signaling pathway suggests strategies for developing targeted therapies including mTOR inhibition, which is being evaluated in clinical trials.

CONCLUSIONS

The surgery had excellent outcome for tuberous sclerosis provided timely decision is taken to treat the tumor and associated hydrocephalus most of these patients will lead ventriculoperitoneal shunt or EVD as an emergency step to save the life.

Address for Correspondence:
Dr. M. Afzal Sheikh
Department of Neurosurgery, Sheikh Zayed Hospital
Rahim Yar Khan
Cell: 0345-5571056

REFERENCES

1. Boehler A, Speich R, Russi EW, Weder W. Lung transplantation for lymphangioleiomyomatosis. N Engl J Med. Oct. 24, 1996; 335 (17): 1275-80.
2. Oabora SL, Jazwiak S, Franz DN, et al. Mutational analysis in a cohort of 224 tuberous sclerosis patients indicates increased severity of TSC_2, compared with TSC_1, disease in multiple organs. Am J Hum Genet. Jun 2001; 68 (1): 64-80 (Medline).
3. Bissler JJ, McCormack FX, Young LR, Elwing JM, Chuck G, Leonard JM. Sirolimus for angiomyolipoma in tuberous sclerosis complex or lymphangioleiomyomatosis. N Engl J Med. Jan 10, 2008; 358 (2): 140-53 (Medline).
4. Krueger DA, Care MM, Holland K, et al. Everolimus for sub-ependymal giant – cell astrocytomas in tuberous sclerosis. N Engl J Med. Nov 4, 2010; 363 (19): 1801-11 (Medline).
5. Curatolo P, Verdecchia M, Bombardieri R. Vigabatrin for tuberous sclerosis complex. Brain Oev. Nov. 2001; 23 (7): 649-53 (Medline).
6. Franz DN, Tudor C, Leonard J, et al. Lamotrigine therapy of epilepsy in tuberous sclerosis. Epilepsia. Jul 2001; 42 (7): 935-40 (Medline).
7. Gates J, Jordan JE. Tuberous sclerosis in old age. South Med J. Aug 1978; 71 (8): 974-6 (Medline).
8. Beltramello A, Puppini G, Bricolo A, et al. Does the tuberous sclerosis complex include intracranial aneurysms? A case report with a review of the literature. Pediatr Radial. Mar 1999; 29 (3): 206-11 (Medline).
9. Dabora SL, Franz DN, Ashwal S, et al. Multicenter phase 2 trial of sirolimus for tuberous sclerosis: kidney angiomyolipomas and other tumors regress and VEGF–D levels decrease. PLoS One. 2011; 6 (9): e23379 (Medline).
10. Hancock E, Osborne JP. Vigabatrin in the treatment of infantile spasms in tuberous sclerosis: literature review. J Child Neural. Feb 1999; 14 (2): 71-4 (Medline).
11. Willmore LJ, Abelson MB, Ben – Menachem E, Pellock JM, Shields WD. Vigabatrin: 2008 update. Epilep-

sia. Feb 2009; 50 (2): 163-73 (Medline).
12. Sampson JR, Attwood D, al Mughery AS, Reid JS. Pitted enamel hypoplasia in tuberous sclerosis. Clin Genet. Jul 1992; 42 (1): 50-2 (Medline).
13. Takanashi J, Sugita K, Fujii K, Niimi H. MR evaluation of tuberous sclerosis: increased sensitivity with fluid – attenuated inversion recovery and relation to severity of seizures and mental retardation. AJNR Am J Neuroradiol. Oct 1995; 16 (9): 1923-8 (Medline).
14. Franz DN, Leonard J, Tudor C. Rapamycin causes regression of astrocytomas in tuberous sclerosis complex. Annals of Neurology. March 2006; 59 (3): 490-498 (Medline).
15. DeKlotz CM, Ogram AE, Singh S, Dronavalli S, MacGregor JL. Dramatic improvement of facial angiofibromas in tuberous sclerosis with topical rapamycin: optimizing a treatment protocol. Arch Oermatol. Sep 2011; 147 (9): 1116-7 (Medline).
16. Caompsano SE, Major P, Halpern E, Thiele EA. Vigabatrin in the treatment of childhood epilepsy: a retrospective chart review of efficacy and safety profile. Epilepsia. Jul 2008; 49 (7): 1186-91 (Medline).
17. Parisi P, Bombardieri R, Curatolo P. Current role of vigabatrin in infantile spasms. Eur J Paediatr Neurol. Nov 2007; 11 (6): 331-6 (Medline).
18. Glauser TA. Topiramate. Epilepsia. 1999; 40 Suppl 5: S71-80 (Medline).
19. Avellino AM, Berger MS, Rostomily RC, et al. Surgical management and seizure outcome in patients with tuberous sclerosis. J Neurosurg. Sep 1997; 87 (3): 391-6 (Medline).