Tuberous Sclerosis Complex : A Review with a Study of Eight Cases

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Summary

This paper reviews the subject of tuberous sclerosis complex and presents data in eight cases of this condition, admitted to Hospital Universiti Sains Malaysia over a period of 8.5 years. The average age at presentation was 53 months. Seizures were the most common presenting feature. Male to female ratio was 3:1. Family history was present in four patients. All of the patients had one or more skin lesions. Six of them had retinal hamartomas. Cardiac tumours were found in two patients. Multiple subependymal hamartomas were detected in six patients. Two patients had renal angiomyolipomas. A high index of suspicion and a detailed physical examination is required to diagnose this rare disorder.

Key Words: Tuberous sclerosis complex, Malaysia, Etiology, Pathophysiology, Clinical features, Diagnosis, Management

Introduction

Tuberous sclerosis complex (TSC) is an autosomal dominant disorder of cellular differentiation and proliferation that can affect the brain, skin, heart, kidneys and other organs[1,2]. Many of the clinical manifestations of TSC result from hamartomas in the affected organs; in addition, abnormal neuronal migration causes neurologic impairment[3]. Clinical expression of TSC is variable, even among the affected members of the same family[4,5,6,7].

Although it has been studied clinically and biochemically for many years the cause as well as pathophysiology of TSC remains unknown[8]. No cell or structural abnormality, enzyme deficiency or molecular defect has been identified in affected individuals[9].

Genetic linkage analysis provides clues to the aetiology of this disease. Genetic linkage of a gene for TSC to loci in 9q32-9q34 has been reported[8,10] but is not a universal finding. Linkage to loci on 11q have also been reported[11]. Based on the findings of third gene locus for TSC on chromosome 12q22-24, disorders of biochemical pathways of phenylalanine hydroxylate, tyrosine and dopamine-beta-hydroxylase might be involved in the pathogenesis of TSC[12].

Like many autosomal dominant disorders, TSC is characterised by phenotypic variability[11,13,14,15] and a high spontaneous mutation rate. Estimates of the frequency of spontaneous mutation range from 56-86% depending in part on the completeness of a family's evaluation[16,17,18,19]. Unfortunately it is currently

impossible to absolutely exclude the diagnosis of TSC in parents of affected children. A number of investigations have been proposed to investigate parents and siblings which include retinal examination (with pupillary dilatation), a thorough inspection of the skin (using an ultraviolet light), renal ultrasound, cranial CT or MRI, and echocardiography. This paper reviews the subject of TSC and presents data on eight cases of this condition admitted to Hospital Universiti Sains Malaysia (HUSM), Kubang Kerian, Kelantan.

Materials and Methods

A retrospective search of hospital records for 8.5 years (lst May 1985 to 30th October 1993) was conducted and the records of the patients diagnosed to have TSC were studied. Six of the eight patients were managed by at least one of the authors. The diagnoses were reviewed following the criteria laid down by American National Tuberous Sclerosis Association for definite and presumptive diagnosis of TSC[20].

Results

Patients

During the period of 8.5 years (lst May 1985 to 30th October 1993) a total of 54,842 patients were admitted to the paediatric and neonatal wards of Hospital Universiti Sains Malaysia and eight were diagnosed to have TSC. Six were males and two were females. The average age at the time of diagnosis was 53 months (six months to 9.5 years). The average age at the time of onset of symptoms was 26 months (20 days of life to five years old). Family history was positive in half of the patients.

Clinical features

Clinical features of our patients are summarised in Table I and are described below.

Cutaneous features

All of our patients had one or more cutaneous lesions. Hypopigmented macules (ash leaf lesions) (Fig. 1) were the most common skin lesions (6 out of 8 patients). Adenoma sebaceum (Fig. 2) was seen in five patients. Shagreen patch (Fig. 3) was noted in one patient. Cafe au lait spots were seen in half of the patients. None of our patients had forehead fibrous plaque, poliosis of the scalp or eye lashes.

Ophthalmic features

Six of eight patients were examined by an ophthalmologist and all were found to have bilateral

Table I
Clinical profile of tuberous sclerosis complex in two studies

	Rochester study[2]	Present study
Duration of study	30 years	8.5 years
Number of patients	8	8
Age at diagnosis		
<5 years	4	4
>5 years	4	4
Sex		
Male	5	6
Female	3	2
Family history of TSC	2	4
Skin		
Hypomelanotic macules	8	6
Facial angiofibroma	4	5
Shagreen patch	2	1
Retinal phakoma	2	6/6*
Central nervous system		
Seizures	4	7
Mental retardation	2	4
Spastic diplegia	1	1
Quadreplegia	1	1
Abnormal CT scan	6/6*	6/6*
Abnormal EEG	?	5/5*

** number of patients who had the particular examination done*

hamartomas. Of these, six were flat and six elevated lesions (Fig. 4). Hypopigmented iris was noted in one patient. Two patients had a small tumour of the skin of the eyelid. One of these patients also had nystagmus. Biopsy of these tumours was not obtained.

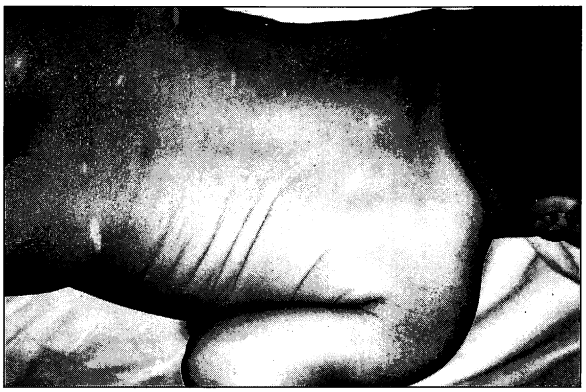

Fig. 1: Hypopigmented macules were the most common skin lesions

Fig. 2: Adenoma sebaceum was seen in five patients

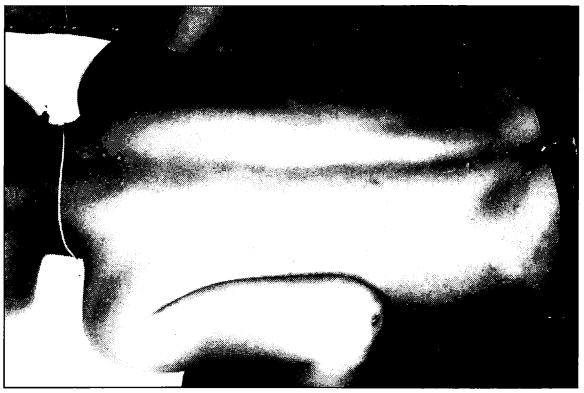

Fig. 3: The Shagreen patch seen in one patient

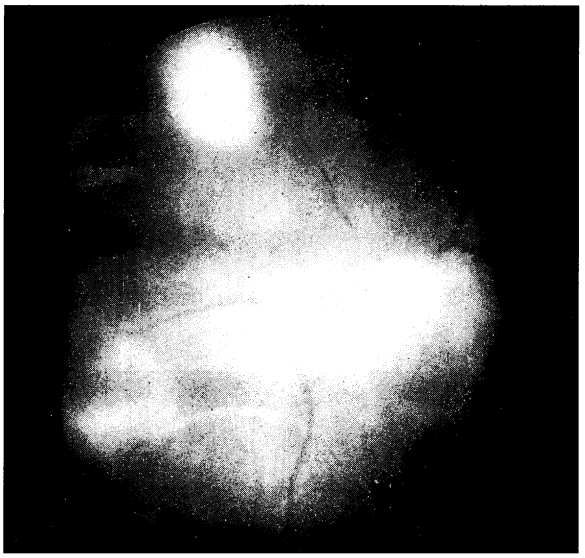

Fig. 4: Lesions on bilateral hamartomas

Renal features

A small angiomyolipoma of 5mm diameter, not visible on ultrasound examination, was detected by CT scan near the upper pole of the right kidney of one patient. Another patient had an angiomyolipoma of both kidneys detected by ultrasound examination.

Neurological manifestations

Seven of eight patients presented with convulsions. Seizures were generalised in six patients. One patient had right sided seizures and hemiplegia. Four patients were mentally retarded with delayed milestones and abnormal findings on neurological examination. One patient had bulbar palsy.

Cardiovascular system

Echocardiographic examination was done in four patients, two of them were found to have a pedunculated growth in the right ventricle (Fig. 5). Both were asymptomatic.

Computed tomography scan (CT Scan)

CT scan of brain was done in six patients: multiple subependymal hamartomas along the wall of lateral

ventricles were present in all (Fig. 6). The majority of these lesions were calcified, their size varying from 1 to 10 mm. None of the patients had hamartomas around the third ventricle or in the cerebellum. There was no evidence of cerebral atrophy or obstruction of the ventricles. Two patients had a large calcified (1 and 1.6cm respectively) nodule in the anterior parietal area, one on the right and other on the left lobe. One patient had small hypodense areas in temporal and parietal lobes, indicating formation of new hamartomas.

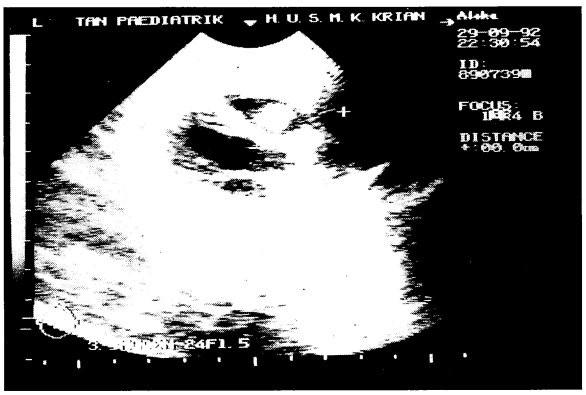

Fig. 5: Pedunculated growth in right ventricle

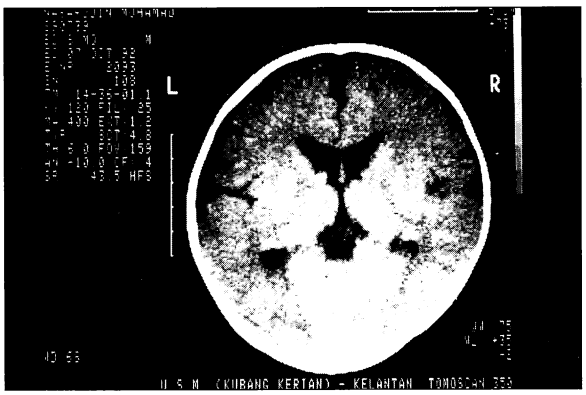

Fig. 6: Subependymal hamartomas along the wall of lateral ventricles

Electroencephalogram (EEG)

EEG was recorded in five patients. All of the five children had generalised multifocal epileptic discharges seen throughout the entire recordings. Typical hypsarrhythmias were seen in two patients. Burst-suppression pattern was noted in recordings of two children, both were six months old. It is interesting to note that one child who presented with a seizure at two months of age had a normal EEG which changed to typical hypsarrhythmia at six months of age (Fig. 7).

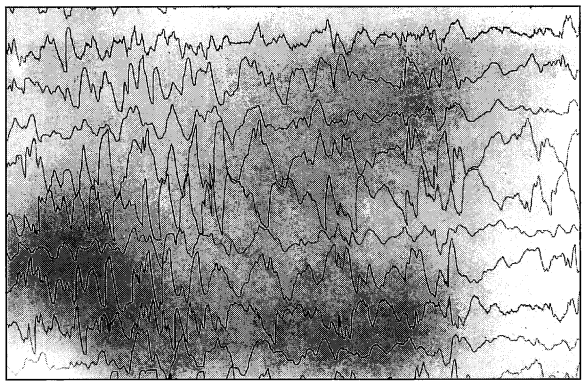

Fig. 7: Typical hypsarrhythmia seen at six months.

Treatment and follow-up

Many different anticonvulsants namely phenobarbitone, clonazepam, sodium valproate, phenytoin, ACTH, prednisolone and carbamazepine were used singly or in different combinations to control the fits. Complete control of fits was achieved in only two patients, four showed a partial response and there was no improvement in one patient.

No specific treatment was offered for cutaneous lesions, cardiac and renal tumours or ophthalmic abnormalities aside from physiotherapy and occupational therapy when indicated. All except one patient were followed in HUSM at the time of this study and the period of follow-up ranged from one to 10 years.

Discussion

Epidemiology

Because of the variation in gene expressivity between affected individuals, both from within the same family and from different families, epidemiological studies usually underestimate the prevalence of the disease. Furthermore patients who die very young with an obstructive cardiac rhabdomyoma, or in renal failure from an angiolipoma or cystic kidneys or both, or succumb inutero to cardiac failure (hydrops foetalis)

are not always diagnosed or included in prevalence studies. Consequently the prevalence must be greater than estimated. Lack of awareness among the primary health care providers, social and health education status of the affected families and the strong influence of traditional healers in the region makes it very difficult to estimate the prevalence of TSC in Malaysia and many developing countries. Table II shows the prevalence rate reported in different studies.

Table II
Prevalence of tuberous sclerosis complex

Country	Ref*	Prevalence
Poland	19	1:23000
Switzerland	73	1:8334
Rochester	74	1:9407
England	75	1:29000 (<65 years old)
		1:21500 (<30 years old)
		1:15400 (<5 years old)

** = Reference number*

Diagnostic criteria

The extreme clinical variability of TSC and the absence of population based studies to determine the frequency of individual physical findings in the general population make it difficult to develop reliable diagnostic criteria. However there seems to be an agreement in the literature regarding criteria for definite and presumptive diagnosis[9,20]. All our patients fulfilled the criteria for "definite" TSC.

Antenatal diagnosis is usually not possible but rarely a presumptive diagnosis can be made by the ultrasonic demonstration of a foetal cardiac tumour[21,22] or the demonstration of multiple subependymal nodules and cortical tubers by MRI[23].

Clinical features

TSC can manifest at any age. Multiple subependymal nodules are shown to be present at least at 28 weeks of gestation[24] and heart and brain tumours in the neonatal period[25]. Late onset epilepsy has also been reported[26]. The average age at the time of diagnosis in our series is 53.4 months (6 months to 9.5 years). The interval between the first presentation and diagnosis of TSC ranged from 0 to 69 months with average of 27 months, suggests a lack of awareness about the illness in the community and primary health care providers.

Cutaneous features

Hypopigmented macules were present in 75% of our patients. These lesions have been reported in up to 98% of patients[27,28] and are often visible at the time of birth[29,30] especially with ultraviolet light. They may also appear in infancy or childhood. Ash leaf spots range in size from 2mm to 12cm with most lesions being between 1 to 3cm. Less commonly ash leaf spots present in a segmental distribution or as multiple confetti-like lesions, 2 to 4 mm in size[31,32]. Poliosis of the scalp hair, eyebrows or eyelashes has probably similar significance. Ash leaf spots occur most commonly on the posterior trunk where their long axes is orientated in a transverse direction; this is in contrast to the extremities, where the orientation of the lesion is cephalocaudal.

Facial angiofibromata (adenoma sebaceum) are seen in 70-83% of reported cases and consist of vascular or connective tissue elements. Typically these lesions extend across the nose and down the nasolabial folds towards the chin and begin as reddened papular lesions in 4-10 years old children and then gradually enlarge. Fibromas in mouth were not found in this series but have been reported in up to 50% of cases on the scalp, neck and axilla[33]. They have been seen even in the newborn infants[34] and have appeared as late as 20 years of age[35]. In our series 62.5% of patients had these lesions.

Only one (12.5%) of our patients had a shagreen patch. The shagreen patches present as a flesh toned plaques or confluent papules with the appearance of pigskin or goose flesh and are slightly raised with irregular borders. Other reports described shagreen patches in 20-83% of patients[33]. These connective tissue nevi are often located on the back or flank region and usually appear between the ages of 2-5 years.

Periungual or subungual fibromas have been described in 19-52% of cases, most commonly in women after puberty[33,36,37]. They are seen more often on the toes

and are associated with renal hamartomas[35,37]. They may regrow after removal. None of our patients who were all relatively young showed these lesions.

A fibrous plaque may be seen on the forehead or scalp. Histological examination of lesions like the adenoma sebaceum reveals angiofibroma. It may be present at birth or appear in neonatal period and be diagnostic for TSC[33]. On the scalp it may be associated with alopecia and may be surrounded by poliosis. None of our patients had these lesions.

Cafe au lait spots are said not to be associated with TSC[38] but in our series 50% of the patients had these lesions, which may be an important variation in our population.

Ophthalmic features

The ophthalmic manifestations of TSC include retinal and non-retinal features. Retinal abnormalities are seen in 50-87% of cases[39,40].

Several types of retinal lesions occur. Plaque like hamartomas and achromatic areas are more common. The retinal hamartomas are astrocytic tumours with a tendency to calcify. Two or more retinal astrocytomas are considered specific for TSC. Six of our patients were examined by an ophthalmologist and all of them had retinal hamartomas. One of them had hypopigmented iris. This abnormality is seen only occasionally[40,41,42]. Like the hypomelanotic skin lesions the significance of these iris lesions lies primarily in their implication for establishing a diagnosis.

A large retinal lesion may cause visual impairment while progressive visual loss can occur in association with hydrocephalus. Giant cell astrocytoma of the retina in TSC has recently been reported[43].

Renal features

TSC in kidney is expressed principally as renal cysts and angiolipomas. These abnormalities may occur separately or together and both are frequently multiple and bilateral. Renal angiolipoma occurs in 50-80% of TSC patients[44] and at least half of the patients with these tumours have other evidence of TSC[45]. Bilateral tumours are common and two or more lesions are often present in patients with TSC[46]. Symptomatic renal tumours are less common in younger children than adults. None of our patients had renal symptoms including the two who were found to have angiolipomas.

The cysts involve predominantly the superficial renal cortex and have a hyperactive and eosinophilic epithelial lining that is unique to patients with TSC and is therefore distinguishable from polycystic kidney[47].

Severe cystic disease can cause renal insufficiency, hypertension and uremia; large angiolipomas predispose to life threatening haemorrhage. Symptoms of haematuria and abdominal or flank pain have been described[48,49]. Renal failure may result from bilateral obstruction of the ureters by adjacent tumours or when much of the normal renal parenchyma is displaced by tumours or cyst. Renal malignancies have been reported in as many as 43% of patients[50].

Neurological features

Seizures occur in an estimated 80-90% of recognised patients. The most common type of generalised seizures in children are infantile spasms and myoclonic seizures followed by tonic, atonic and atypical absence seizures. Tonic-clonic seizures are commonly seen after the first year of life and are associated with or replace the other types. Infantile spasms are rare after the age of four years. Of patients with seizures, 84% are generalised, 29% partial, 15% both types[51]. Two of our eight patients had infantile spasms. Generalised seizures were seen in 87.5% of cases. Focal fits were present in only 14.3% of the patients. Hemiplegia and other focal deficits may be seen occasionally. One patient in our series presented with hemiplegia.

There is correlation between the occurrence of fits early in life and the subsequent finding of mental retardation. Approximately 60% of TSC patients are mentally retarded, but the spectrum of intellectual impairment varies from borderline to profound dysfunction. Autism and various behaviour disturbances are common.

Motor deficit has been infrequently recognised. Spastic

diplegia usually in association with severe mental retardation, hemiplegia, monoplegia, triplegia and atonic diplegia have all been reported[1].

Giant cell astrocytoma occur in 6 to 14% of patients with TSC[42,52] and are more likely to develop during the first two decades[53]. Contrast enhancement on CT or MRI helps to distinguish a giant cell astrocytoma from the other cerebral lesions of TSC. Enlargement of the tumour may present as a new focal neurological deficit, increased intracranial pressure, behaviour change or loss of seizure control. Acute deterioration may result from sudden obstruction of the ventricular system or from haemorrhage within the tumour[54]. Removal of these lesions is advisable if the tumour is enlarging or symptomatic.

Cardiac features

Two out of four patients examined by echocardiogram showed pedunculated tumours in the right ventricle. Both of them were asymptomatic. Up to 66% of patients with TSC have a cardiac rhabdomyoma[55]. These hamartomas tend to be multiple and their size and number tend to decrease with age[56]. Spontaneous regression of cardiac tumours is known[57].

At least half of the patients with a cardiac rhabdomyoma have other evidence of TSC[58]. Most patients with these cardiac tumours remain asymptomatic; those with cardiac dysfunction typically present soon after birth with heart failure[30,59] caused either by obstruction from an intraluminal tumour or replacement of normal myocardium with tumour. Cardiac tumours are evident with ultrasonography or more recently with MRI[60]. Two dimensional echocardiography is especially helpful in infants and children below two years of age[28,57]. Cardiac arrhythmia without a demonstrable tumour has been reported[38].

Cardiac symptoms develop through one of the three possible mechanisms : (a) obstruction of the blood flow by an intracavity tumour in the outflow tract of the right or left ventricle. (b) cardiac arrhythmias caused by septal myoma interrupting the conduction system. (c) impairment of ventricular wall contractibility resulting from myocardial replacement by noncontractile intramural tissue[61]. Intrauterine cardiac failure may be the cause of hydrops foetalis[62], still birth[63] or neonatal death[24].

Cardiac arrhythmias associated with rhabdomyoma include atrial or ventricular tachycardia, Wolff-Parkson-White syndrome, junctional ectopic beats, complete heart block and ventricular fibrillation.

Respiratory system

Pulmonary involvement occurs in only 1% of TSC patients and is five times more common in girls[39]. Pulmonary failure, dyspnoea, hemoptysis, and spontaneous pneumothorax are typical of pulmonary TSC. Although the symptoms seldom occur before the 3rd or 4th decade, the prognosis for five-year survival once symptoms begin is poor[39].

The symptoms may vary according to the mechanism involved and may be result of (a) spontaneous pneumothorax (b) pulmonary failure with hyperinflation of lungs and (c) pulmonary hypertension and corpulmonale.

Spontaneous pneumothorax is recurrent and is manifested by sharp chest pain often associated with blood streaked sputum. A chest radiograph will reveal a partial pneumothorax and there may be increased markings in a reticular pattern that gives a honeycomb appearance to pulmonary parenchyma. None of our patients had respiratory problems and radiographs of chest were normal in all of them.

Computed tomography scan (CT Scan)

Imaging studies are reported to be positive in 92.5% of cases. CT scan is more useful in detecting subependymal nodules, while MRI shows the number and location of cerebral cortical and subcortical lesions more accurately[64].

The radiographic hallmark of TSC is the calcified subependymal nodules best demonstrated by CT scan[52,65,66]. The calcification tends to develop with time and because of this the lesion may not be apparent in infants. All our six patients who had the CT scan examination showed abnormalities.

CT does not correlate with the clinical severity of TSC but a patient with numerous large cortical or subcortical lesions on MRI is more likely to have severe mental retardation and intractable seizures[67,68,69].

Electroencephalogram

All five of our patients who had an EEG done had positive findings. Abnormal EEGs are reported to be found in 90% of recordings. The EEGs tended to improve with age[28]. Our findings are consistent with previous reports that these abnormalities are nonspecific and offer no help in the diagnosis of TSC.

Treatment

No treatment is usually required for hypomelanotic macules or a shagreen patch. Laser therapy can minimize the cosmetic effect of facial angiofibroma, although improvement is usually transient.

Large ungual fibromas that interfere with shoe fitting or become easily traumatised should be removed; otherwise treatment is usually unnecessary.

Although a large retinal lesion may cause visual impairment, progressive visual loss does not usually occur. In general patients with TSC require only routine eye care, unless a specific problem is identified.

The choice of antiepileptic drug depends on the patient's age and seizure type. Carbamazepine for focal onset seizures and valproic acid for generalised seizures is usually effective. ACTH or valproic acid sometimes controls infantile spasms. Phenobarbitone is occasionally useful. Phenytoin and carbamazepine were the most effective anticonvulsants in our patients.

Surgical removal of symptomatic intraluminal cardiac tumour may be life saving if the patient is stable enough to tolerate the surgery. For patients with intramural tumours digoxin and diuretics may allow the patients to stabilize. Some neonates with heart failure eventually improve, although their overall prognosis is poor[58]. As TSC patients are prone to have pneumothorax, positive pressure ventilation during anaesthesia should be avoided or monitored closely[70].

Course and prognosis

The course of TSC depends on the affected organ(s) and it cannot be predicted from the clinical expression, severe or mild. It is therefore necessary to assess the involvement of each affected organ and in particular the kidneys, lungs, heart and brain.

Judging by post-mortem findings in patients with TSC, the renal system is almost always involved and is the major cause of death in these patients[71].

In a series, of 40 patients who died of TSC, one baby died of cardiac failure due to cardiac rhabdomyoma and other of rupture of an aneurysm of the thoracic aorta. Eleven patients died of brain tumour and 4 patients (who were 40 years or older) died of lymphangiomatosis of the lung. Thirteen patients with severe mental retardation died of either status epilepticus or bronchopneumonia[72].

Patients with TSC need life long follow-up for early detection of potentially life-threatening complications.

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