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**CHARACTERISTICS OF TUBEROUS  
SCLEROSIS COMPLEX IN A SOUTH AFRICAN  
COHORT: DESCRIPTION AND PARENTAL  
UNDERSTANDING.**

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Health of the University of Cape Town in partial fulfilment of the  
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## DECLARATION

I, *Pauline Wangechi Samia* hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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## ABBREVIATIONS

ADHD	Attention deficit hyperactivity disorder
CT scan	Computer Tomography Scan
DNA	Deoxyribonucleic Acid
DQ	Developmental quotient
FLAIR	Fluid attenuated inverse recovery
fMRI	FLAIR MRI
ECG	Electrocardiogram.
EEG	Electroencephalogram.
IQR	Inter-quartile range
Kb	Kilo bases
Kg	Kilograms
MRI	Magnetic resonance imaging
mTOR	Mammalian target of rapamycin kinase
P13K	Phosphoinositide 3-kinase: a signalling system which phosphorylates tuberin.
PDD	Pervasive developmental disorder
PKD	Polycystic kidney disease
Rheb	Ras homologue enriched in brain (an intracellular signalling protein)
RXH	Red Cross Hospital
SD	Standard deviation
SEGA	Subependymal giant cell astrocytomas
TSC	Tuberous Sclerosis Complex
USA	United States of America

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## **ABSTRACT**

### Introduction

Tuberous sclerosis complex (TSC) is a genetically inherited condition that manifests with benign non-invasive tumours or hamartomas in multiple organ systems. The condition is of autosomal dominant inheritance with an estimated incidence of 1 in 6000 live births. Population based studies estimate the prevalence of TSC to be 1 per 14, 492 population.

TSC has myriad presentations but 80 to 90% of these children have seizure disorders. The prevalence of learning disabilities in children with TSC ranges from 38% to 80%. Pervasive developmental disorders (PDD) and attention deficit hyperactivity disorder have been identified in half of the children with TSC. Cutaneous manifestations occur in more than 90% of TSC patients. Cortical tubers, cardiac rhabdomyomas and renal angiomyolipomas are other lesions associated with TSC in children.

Currently TSC has no cure and associated complications manifest with advancing age. Parents are faced with the challenge of life long care for these children. Half of the parents of children with TSC suffer significant psychological stress. Child specific factors, health literacy, and social stability are some factors known to impact on parental understanding of a child's chronic illness. Data specific to parental understanding of TSC are limited.

### Methodology

A retrospective case note review was performed to obtain the patient demographic and clinical presentation data. A prospective observational study provided the parental background characteristics and information on their understanding of TSC.

### Results

A total of 31 patient case notes were included in the review. The median patient age at the time of data was 132 months (IQR 96.00). The male: female ratio was 4:1.

Seizures were observed in 27 patients (87.1%). Infantile spasms were reported in 3 (9.6%) patients while partial seizures occurred in 11 (35.5%) patients. More than one anticonvulsant was required in 15 (48.4%) of the 27 patients with seizures.

Fourteen (53.8%) had global developmental delay. Two children (6.4%) were both hyperactive and aggressive and six (19.3%) were considered hyperactive. Aggressive behaviour was observed in four (12.9%) other children.

Parents of 21 patients gave consent to participate in the study. The median parental age was 38 years (IQR 10.5). Seven parents (33.3%) had attained a primary level of education. Secondary education was attained by ten parents (47.6%) and three (14.3%) had received tertiary education.

A statistically significant difference,  $p$  value = 0.001, was observed in the change in the level of knowledge on comparison between the parent group that received a leaflet and the one that did not. A parental level of education of grade 8 was associated with a significantly higher baseline knowledge score ( $p$  value = 0.045) and a significantly greater change in the level of knowledge score ( $p$  value = 0.003).

No association was detected between a parent's duration of clinic attendance and the baseline level of knowledge ( $p$  value = 0.63) There was no association between a parents baseline level of knowledge and their assessment of the impact of TSC on their child. ( $p$  value = 0.61)

#### Conclusions and recommendations

The clinical profile of the cohort of children seen at the Red Cross Children's Hospital is similar to that of other cohorts described in literature. Parental understanding of TSC can be improved by provision of written information for those with at least a grade eight level of education. The information leaflet used in this study can be used to educate parents of children with TSC.

## INTRODUCTION

Tuberous sclerosis complex (TSC) is a genetically inherited condition that manifests with benign non-invasive tumours or hamartomas in multiple organ systems, mainly skin, central nervous system, heart, kidneys, eyes and lungs resulting in variable clinical presentations.<sup>1-4</sup> The condition is of autosomal dominant inheritance and is one of the most common heritable single gene disorders in children with an incidence of 1 in 6000 live births<sup>1-3</sup> It is estimated that two thirds of new TSC patients without a family history are new mutations.<sup>1,4-7.</sup>

Population based studies are currently considered to provide the most accurate estimates of the prevalence of TSC.<sup>8</sup> Initial studies conducted in 1956 by Stevenson and Fischer in a population of Northern Ireland estimated the prevalence to be 1 per 150,000 population while that conducted by Singer in a Chinese population in 1971 estimated the prevalence to be 1 per 70,000 population.<sup>8</sup> Shepard and colleagues studied a population that included 100,000 people in Olmstead County in Minnesota, USA and determined the prevalence of TSC to be 1 per 14,492 population. Due to the comprehensive medical record system used, this study is considered to provide the most accurate estimation of the prevalence of TSC.<sup>8,9.</sup>

Patients with TSC may be identified at any age though historically the average age at presentation is five years.<sup>4</sup> Indeed, earlier studies indicate many cases of TSC were only identified in late childhood and adulthood.<sup>4,10</sup> With increasing awareness regarding the presentations of TSC, improved availability of prenatal ultrasound, magnetic resonance imaging (MRI) and prenatal genetic testing the mean age at which a diagnosis of TSC is made is expected to reduce from the reported five years.<sup>4,8,11,12</sup>

TSC has a myriad of clinical presentations that evolve with increasing age. At birth, many neonates with TSC may not be detected as the only external manifestation that may be present is hypomelanotic macules.<sup>4,8,13</sup> The most useful criteria for diagnosis of TSC in infants have been found to be

hypomelanotic macules and epilepsy.<sup>4,12</sup> Beyond infancy, seizure disorders are apparent in 80% to 90% of children with TSC.<sup>1-4, 6-13.</sup>

Approximately half of all patients with tuberous sclerosis have some degree of cognitive impairment.<sup>1-3,6-8,10</sup> Developmental, behavioural and sleep disorders are common in TSC cohorts with up to half of whom have autistic spectrum disorders.<sup>1-3,6,10,14-17.</sup> The age at which specific cognitive and behavioural problems present varies, with intellectual impairment evident before age three years, hyperactivity between three and eight years while anxiety and depression are commonly observed in adolescence.<sup>15</sup>

Parental perceptions on various chronic illnesses including epilepsy in children have been widely published but data from parents of children with TSC are few.<sup>18</sup> It is known that parental understanding of a child's chronic illness influences their ability to cope and their interaction with the health system.<sup>19-24</sup> Further, it is known that parental perceptions of a child's illness may in turn be influenced by factors such as the severity of a child's illness as well as the stability of the parental social support systems.<sup>25-29.</sup>

Currently TSC has no known cure. Active management of immediate problems with careful anticipatory evaluations for expected complications remains the mainstay of care for children with TSC. Data on African cohorts with TSC are limited and disease evolution in this part of the world has not been extensively studied. This study would therefore make a useful contribution to the existing body of knowledge by providing a description of the Red Cross Children's Hospital TSC cohort. An exploration of the understanding their parents have of this chronic condition would not only provide information but would also educate the health service providers on ways to better meet the educational needs of parents of children with TSC.

## LITERATURE REVIEW

### Historical aspects of TSC

The earliest known graphic description of TSC dates back to 1835 in an atlas of skin diseases compiled by Pierre François Rayer in which a young man's face is shown with small papules that bear the characteristic distribution and appearance of facial angiofibromas.<sup>8</sup>

In 1862 Friedrich Daniel von Recklinghausen described the pathological findings of a neonate who had died shortly after delivery. The post-mortem findings included multiple cardiac tumours and 'cerebral scleroses'.<sup>1,8</sup> A detailed report of the neurological presentation of TSC was first provided by Bourneville in 1880 when he described a young girl who had presented with seizures and learning disabilities at the age of two years. This child was later found to have facial skin lesions and a spastic right hemiplegia in adolescence. Her brain was described as having "tuberous scleroses of the cerebral convolutions"<sup>1,8</sup>

Voigt in 1908 provided the frequently quoted triad of manifestations of TSC comprising of mental retardation, intractable epilepsy and adenoma sebaceum. Voigt also included cardiac and renal tumours as part of the disease description.<sup>1,3,7,8</sup>

In 1932 Critchley and Earl reported "white spots" (hypomelanotic macules) in 29 patients with TSC and also described autistic behaviour as part of the condition.<sup>8</sup> In 1942 Moolten recognized the complex pathological nature of the lesions that occur in this condition and named it "the tuberous sclerosis complex", the name by which the condition is now known.<sup>8</sup>

The genetic nature of TSC was first elucidated by Kirpicznik in 1910, who reported a family with three generations of affected individuals and described the condition in identical and fraternal twins.<sup>8</sup>

The first genetic linkage analysis report that identified a probable TSC gene on chromosome 9q34 was published in 1987.<sup>8</sup> The TSC1 gene was cloned and its product confirmed to be hamartin by van Slegtenhorst and colleagues in 1997. A second TSC locus (TSC2) was identified on chromosome 16p13 in 1992 by Kandt and colleagues. This gene was cloned and its product confirmed to be tuberin in 1993<sup>8</sup>

### **The genetic basis of TSC**

TSC is caused by a mutation in one of two tumour suppressor genes TSC1 and TSC2 located on chromosomes 9 (9q34) and 16 (16p13) respectively.<sup>1,2,6-8,30</sup> Following identification of the TSC1 and TSC2 genes nearly 500 different mutations in these genes have been characterised.<sup>1,6,7,30</sup> A mutation of one of these two genes is identified in 60 to 85% of TSC patients where resources allow genetic testing.<sup>1,7,11,31,32</sup> A similar distribution of mutations of the TSC1 and TSC2 genes has been described among familial cases. Among sporadic cases TSC2 mutations are more frequent.<sup>6,7,13,32</sup>

The TSC1 gene spans 50kb (kilobases) of genomic DNA and contains 23 exons. It encodes the protein Hamartin which is widely expressed in normal tissue including brain, cardiac, skin and renal tissues.<sup>8,33,34</sup> Several types of TSC1 mutations have been identified. Fifty percent are small deletions and insertions, 35% are nonsense mutations and less than 5% are large deletions.<sup>31,32,35,36</sup> The exact function of Hamartin remains unknown but it forms a complex with tuberin which participates in cell cycle regulation.<sup>1,6,7,13,30,37,40-42</sup> Most of the TSC1 mutations result in a truncated hamartin protein with loss of cell cycle regulatory function.<sup>36</sup>

The TSC2 gene spans 45 kb of genomic DNA and contains 42 exons<sup>43</sup> The gene is expressed in all normal adult tissues and encodes the protein tuberin which appears to participate in normal brain development and in removal of the normal cardiomyocyte cell from the cell cycle during differentiation of the myocardium.<sup>44</sup>

TSC2 mutations include large deletions and rearrangements in 15%, small deletions and insertions in 35% and nonsense mutations in 20%.<sup>31,32,45</sup> These mutations result in loss of function.<sup>31,32,45</sup> Whereas missense mutations have not been reported for the TSC1 gene they account for 25% of TSC2 gene mutations and do not cause loss of cell cycle regulatory function.<sup>31,32,45-47.</sup>

Tuberous sclerosis is an autosomal dominant genetic disorder with complete penetrance.<sup>1,4-8,48</sup> It is estimated two thirds of new cases without a family history of TSC are new mutations within a family.<sup>1,4-8,49-51.</sup> Two to ten percent of people who carry the TSC gene are not detected by genetic testing due to germ cell mosaicism and this phenomenon may give rise to “new” cases.<sup>1,4-8,49-51</sup>

A loss of heterozygosity for alleles of the TSC1 and TSC2 genes has been described in hamartomas from TSC patients. This observation indicates that two somatic mutations at a cellular level are required to produce the TSC phenotype.<sup>1,30,37,52,53</sup> Though penetrance of the mutant TSC gene is complete, the phenotypic expression of disease varies in individuals even within the same family due to somatic mosaicism.<sup>54-57</sup>

TSC1 mutations were previously reported to be associated with a milder neurological disease phenotype while TSC2 mutations were associated with more severe disease manifestations.<sup>30-32,47,52,53</sup> Subsequent studies have dispelled these initial findings, as both gene mutations have been shown to cause a similar clinical disease presentation.<sup>6,7,14,30,35,40,41,53</sup>

The variety of mutations that occur in each gene and the need for a second mutation in the wild type copy of the gene for expression of the pathogenic manifestations of TSC all contribute to the phenotypic variations observed in TSC.<sup>51,54-61.</sup> Clustering has not been observed to occur in TSC. The condition occurs in all ethnic groups in what is assumed to be a uniform rate across all human populations.<sup>8</sup>

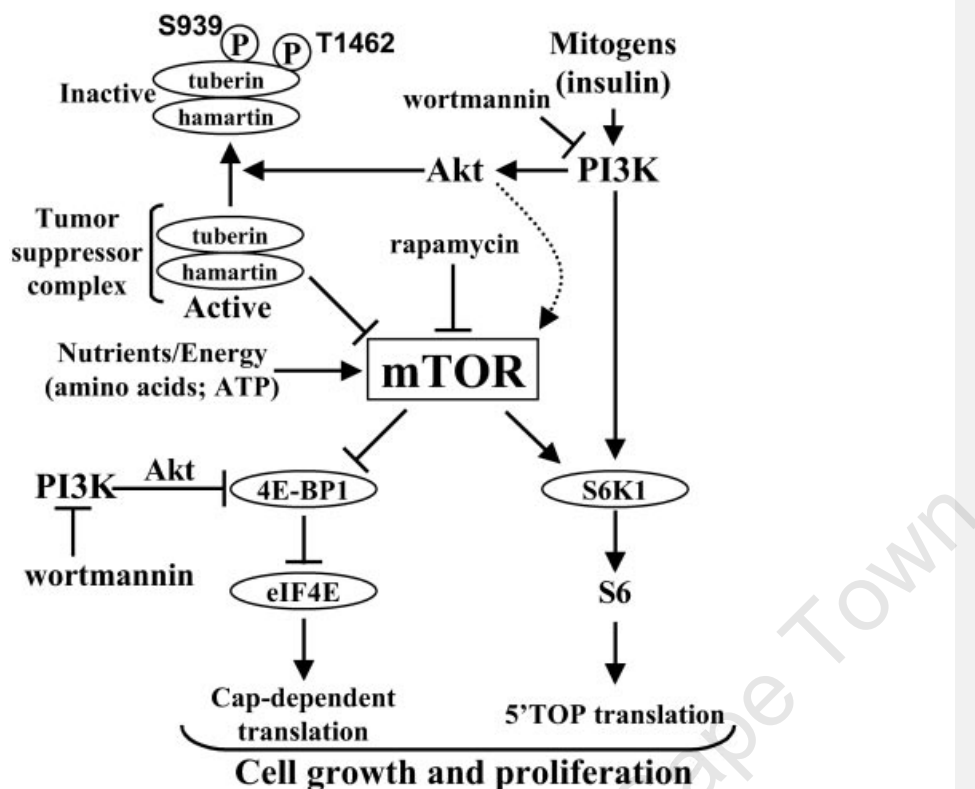
### **Pathogenesis of TSC**

The mammalian target of rapamycin kinase, (mTOR) is an enzyme which belongs to a family of phosphatidyl inositide kinases. mTOR kinase functions to promote protein translation and cellular proliferation under adequate nutritional and energy provisions.<sup>39</sup> Hamartin and tuberin form an intracellular complex that inhibits mTOR.<sup>1,6,7,13,30,37,38,43,47,52,53</sup> mTOR in turn acts via Rheb (Ras homologue enriched in brain) an intracellular signalling protein to inhibit S6 kinase, a ribosomal protein that is key in the protein translation process, thereby effecting negative control of cell growth and differentiation.<sup>1,6,7,13,30,37-42</sup>

In normal cells with intact mTOR signalling, cell growth and proliferation proceeds in the presence of mitogens such as insulin, which activate the P13K (phosphoinositide 3-kinase) signalling system. The P13K system in turn, phosphorylates tuberin through protein kinase B (also known as Akt) and effectively inhibits the ability of the hamartin-tuberin complex to suppress mTOR activity.<sup>7,40,41</sup>

A mutation in either TSC1 or TSC2 results in lack of either hamartin or tuberin therefore the hamartin – tuberin complex is not formed. Lack of this complex allows the cell proliferation cycle to be in a constant state of over activity due to lack of inhibitory regulation of mTOR mediated signalling to downstream targets. Over activity of the cell cycle results in the development of hamartomas.<sup>7,13,38-42</sup>

The process by which tuberin and hamartin control cell growth and proliferation is illustrated in the diagram below. (Permission to reproduce granted 20/07/09 by J.Blenis)



Model showing that tuberin-hamartin complexes modulate PI3K dependent signalling through mTOR to both 4E-BP1 and S6K1. Activation of PI3K leads to inactivation of the tuberin-hamartin complex by Akt-mediated phosphorylation of tuberin at Ser-939 and Thr-1462. Inactivation of the tuberin-hamartin complex releases the inhibition of mTOR and allows nutrient-dependent signalling from mTOR to S6K1 and the 4E-BP1-eIF4E complex. As a result, cap-dependent and 5-terminal oligopyrimidine tract (5'-TOP) mRNA-mediated translation are increased. The dotted arrow depicts the finding that Akt phosphorylates mTOR (41).

(Reference: Tee A.R, Fingar DC, Manning BD, et al, Tuberous sclerosis complex1 and 2 gene products functions, together to inhibit mammalian target of rapamycin (mTOR)-mediated downstream signalling. Proc Natl Acad Sci. 2002; 99: 13571 – 13576.)

The Harmatin-tuberin complex also participates in other pathways including a cell adhesion, cell migration and protein transportation pathways.<sup>7,8,52</sup> It is postulated that loss of hamartin due to TSC1 mutations interferes with normal cell – cell adhesion and intracellular matrix protein adhesion that in turn

compromises cell migration. In the developing brain, loss of normal cell-cell interaction is thought to contribute to the formation of tubers.<sup>8</sup>

### **Diagnostic criteria for TSC**

The current diagnostic criteria for TSC were developed at a consensus conference held in 1998 that took into consideration all known specific manifestations of TSC and improved on previously utilised criteria.<sup>1,2,8,48</sup>

A definitive diagnosis of TSC is based on clinical features that are currently classified as major or minor features. Presence of two major features or one major and two minor features provides a definitive diagnosis of TSC, while presence of one major feature and one minor feature denotes probable TSC.<sup>1,2,8,48</sup> Detection of one major feature or two minor features indicates possible TSC.<sup>1,2,8,48</sup> Epilepsy is not considered one of the criteria due to its low specificity for TSC.<sup>2,48</sup> These criteria are summarised below.

### **REVISED DIAGNOSTIC CRITERIA FOR TUBEROUS SCLEROSIS COMPLEX.<sup>48</sup>**

#### **Major Features**

1. Facial angiofibroma or forehead plaque
2. Non traumatic ungal or periungual fibroma
3. Hypomelanotic macules (three or more)
4. Shagreen Patches
5. Multiple retinal nodular hamartomas
6. Cortical tuber
7. Subependymal nodule
8. Subependymal giant cell astrocytomas
9. Cardiac rhabdomyoma, single or multiple
10. Lymphangiomyomatosis
11. Renal angiomyolipomas

#### **Minor features**

1. Multiple randomly distributed pits in dental enamel
2. Hamartomatous rectal polyps
3. Bone cysts
4. Cerebral white matter radial migration lines

5. Gingival fibromas
6. Non renal hamartomas
7. Retinal achromic patch
8. 'Confetti' skin lesions
9. Multiple renal cysts

Definite Tuberous sclerosis complex

- Two major features or
- One major and two minor features

Possible Tuberous sclerosis complex

- One major feature or
- Two or more minor features

Reference: Roach ES, Gomez MR. Tuberous sclerosis consensus conference: Revised clinical diagnostic criteria. J Child Neurol 1998; 13: 624

Due to the fact that many of the features of TSC appear with advancing age, the utility of the above criteria initially appeared to be limited in infancy.<sup>4,12,60.</sup> However, following the wide dissemination of these criteria, it is now known that the criteria is of definite utility as it provides for a probable or a possible diagnosis in the younger child that can be confirmed later, with emerging features.<sup>2</sup>

Following revision of the diagnostic criteria for TSC, recommendations for further evaluation of patients following determination of a definite, possible or probable diagnosis of TSC were published in 1999.<sup>61</sup> These recommendations promote appropriate follow up, detection of complications and their timely management. They are summarised below.

## SUMMARY OF TESTING RECOMMENDATIONS.<sup>62</sup>

Assessment	Initial testing	Repeat testing
Neurodevelopmental assessment	At diagnosis and school entry	As indicated
Ophthalmic examination	At diagnosis and school entry	As indicated
ECG	At diagnosis	As indicated
EEG	If seizures occur	As indicated
Echocardiography	If cardiac symptoms occur	If cardiac dysfunction occurs
Renal Ultrasound	At diagnosis	Children every 1-3 years
Chest CT	Adult females	If pulmonary dysfunction occurs
Cranial CT	At diagnosis	Children every 1-3 years
MRI Brain	At diagnosis	Children every 1-3 years

Reference: Roach ES, DiMario FJ, Kandt RS, et al. Tuberous sclerosis consensus conference: Recommendations for diagnostic evaluation. *J Child Neurol* 1999; 14: 401 – 407.

### The clinical presentation of TSC

Dermatological features.

Cutaneous manifestations occur in more than 90% of TSC patients, although none of them are pathognomonic.<sup>1,2,4,8,51,62,63</sup> Hypopigmented lesions of varying shapes are common at birth and were found in 51% of infants at diagnosis in one study.<sup>4</sup> They were found to increase in frequency from 89.6% in children below two years, to 97% in children 14 to 18 years in another study.<sup>4,12</sup> Webb *et al* examined a group of children under five years of age with TSC and found all of them to have hypomelanotic macules.<sup>63</sup> Hypomelanotic macules are commonly found on the trunk, extremities and gluteal region.<sup>8</sup> Where hypomelanotic macules are not identified, a wood's

lamp examination may be useful (though this examination was thought to be more useful for evaluation of adult relatives than children).<sup>64</sup>

Facial angiofibromas are smooth nodules that occur on the central part of the face, especially on the nasolabial folds, cheeks and the chin.<sup>1,2,8,12,37,48,65,66</sup> Facial angiofibromas are unique to TSC and are of diagnostic value in children with TSC in whom they appear between one and years (52.8%). There is progressive increase in size and number through to adolescence.<sup>1,2,4,8,12,48,63</sup>

A fibrous plaque is a flesh coloured patch of raised skin of variable size and shape that is usually located on the scalp or forehead.<sup>1,2,8,12,37,48,66</sup> These plaques appear at any age and may be evident at birth with a tendency to enlarge with advancing age.<sup>8,60</sup>

Connective tissue hamartomas, also known as shagreen patches, usually occur in the lumbosacral region at puberty in 48% of those with TSC.<sup>1,2,8,12,48</sup> The lesions are frequently elevated above the surrounding skin, asymmetrical, firm and resemble an orange peel. The number and size of Shagreen patches tends to increase into adulthood.<sup>8</sup>

Non-traumatic subungual or periungual fibromas are fleshy growths that occur around nail beds more frequently on the toes than on the fingers in approximately 20% of those with TSC at adolescence.<sup>1,2,8,12,37,48,66</sup>

Confetti like lesions are multiple small white spots 1-2 mm in diameter that tend to occur over the forearms and lower legs. A higher incidence has been noted in adults (20%) than in children (2.8%).<sup>8</sup>

#### Neurological manifestations of TSC

Epilepsy is the most common presentation in TSC and usually has an onset in childhood. Seventy percent of children have seizures before two years of age.<sup>1-4,6-13</sup> It is estimated 80 – 90% of patients develop epilepsy at some point in their lifetimes.<sup>1-4,6-13</sup> Cortical tubers that can be detected by MRI brain as

high signal intensity areas, represent the epileptogenic foci of epileptic seizures.<sup>6,8,67,68</sup>

Patients with TSC exhibit multiple seizure types. Infantile spasms occur in a third to half of infants with tuberous sclerosis and are a common type of seizure at initial diagnosis. These seizures have a close association with learning disorders.<sup>1-4,6,8,12,69,70</sup> Tuberous sclerosis is the cause of infantile spasms in 10 -20% of those who have this seizure type.<sup>3</sup>

Infantile spasms among children with TSC have been found to be sensitive to Vigabatrin. Overall control of seizure disorders in children with TSC is a management challenge and often calls for additional interventions including surgery, and the ketogenic diet.<sup>1,4,6,8,12,30,37,39,67-74</sup> The natural history of epilepsy in children with TSC tends to be one of progressive seizure frequency and severity.<sup>1,6,8,66</sup> An attendant reduction in the quality of life is observed as a result of intractable seizures and adverse medication side effects.<sup>1,6,8,66</sup> Seizure onset in infancy, presence of multiple seizure types and evolution of new EEG seizure foci are all poor prognostic factors.<sup>6,8</sup>

Neuroimaging in children with TSC demonstrates cortical tubers, subependymal nodules and giant cell astrocytomas.<sup>1-4,6,13,30,37,39,75-79</sup> Cortical tubers are pathognomonic of the disease.<sup>1,36,75-79</sup> Tubers are commonly found in the cerebrum, with 90% occurring in the frontal lobe while subependymal nodules occur in the walls of the lateral ventricles.<sup>1,75,79</sup> Both CT and MRI scans can identify subependymal nodules but MRI fluid attenuated inverse recovery (FLAIR) sequences provide superior demonstration of brain abnormalities in TSC.<sup>1-3,6,30</sup> Subependymal giant cell astrocytomas (SEGA) arise from subependymal nodules in 6 to 15% of subjects with TSC causing progressive neurological deficits.<sup>1,6,30,39,75,79</sup>

The prevalence of learning disabilities in children with TSC ranges from 38% to 80% with those who have infantile spasm being the most affected.<sup>1-3, 6-8, 30,37,38,80,81</sup> Patients with intractable seizure disorders and more than ten cortical lesions detected by non-FLAIR MRI have been found to have poorer

developmental outcomes.<sup>81,82</sup> Cognitive disabilities in TSC range from mild learning disabilities to profound intellectual disability with the eventual outcome being influenced by the extent of the brain abnormality, age at seizure onset and type of seizure disorder.<sup>1,15,83</sup>

Children with cognitive disabilities are at particularly higher risk for behavioural and psychiatric disorders compared to those of normal intelligence. It has been observed 60 to 70% of children with both TSC and global intellectual impairment have one or more behavioural problems while only 20-30% of those with TSC without intellectual impairment have behavioural difficulties.<sup>28,84,85</sup> Classical infantile autism has been identified in 25% of those with TSC while pervasive developmental disorders (PDD) and attention deficit hyperactivity disorder (ADHD) have been identified in 50% of these children.<sup>1-3,6,8,14-17,84-88</sup>

#### Non-neurological manifestations of TSC

Renal manifestations are the next most common presentation after neurological complications. Renal angiomyolipomas are present in up to 80% of TSC patients while renal cysts occur in less than 20%.<sup>1,8,51,89</sup> Angiomyolipomas exceeding four centimetres in diameter carry the risk of life threatening hemorrhage from dysplastic aneurismal vessels.<sup>1,8,30,89</sup> Polycystic kidney disease (PKD) may also occur in TSC patients, reflecting a contiguous gene deletion syndrome. The PKD gene occurs adjacent to the TSC2 gene.<sup>1,8,89</sup> Renal tumours are benign and usually asymptomatic before adolescence.<sup>8,30,37,38,89</sup>

Rhabdomyomas are the chief cardiac manifestation of TSC presenting in 50 to 60 % of children with TSC.<sup>1-4,8,11,89,90,91</sup> They are easily detected prenatally with a maximal size at birth or in early childhood.<sup>1-4,8,11,90,91</sup> Spontaneous regression during the first few years of life occurs.<sup>1,4,8,11,91</sup> Majority of children with cardiac rhabdomyomas are asymptomatic. However, 2-4% of these children have large rhabdomyomas with resultant complications such as valvular outflow tract obstruction, arrhythmia and cardiac failure.<sup>1-4,8,11.</sup>

Ocular manifestations of TSC include retinal hamartomas, optic nerve atrophy, glaucoma, and colobomata of iris, lens and choroid.<sup>8</sup> Retinal hypopigmentation and hyper-pigmentation have also been reported.<sup>8</sup> Depigmented lesions may have a plaque-like centre which obscures the choroidal blood vessels. Retinal hamartomas have been observed in approximately half of those with TSC, but visual disturbances are an uncommon presentation in this condition.<sup>1,2,8</sup> Growth of retinal hamartomas is rare with most lesions remaining stable over several decades.<sup>1,2,8</sup>

### **Parental understanding of TSC and other chronic illnesses in children**

Parents of a child with a chronic illnesses are faced with the challenge of coping with the burden of daily care related to the illness and adjustment to the varying demands the condition places on them.<sup>19</sup> Half of the parents of children with TSC, have been reported to have significant levels of psychological stress especially in relation to seizures, cognitive impairment, psychiatric and behavioural problems in their children.<sup>18</sup>

Depression or concerns regarding signs, symptoms and diagnosis of chronic illness have been reported in parents.<sup>25-29,92-94</sup> Some parents express concern regarding the effect of the child's illness on their own functioning.<sup>38-42,89-91</sup> In previous studies limitations in social and family function as a direct effect of the child's illness have been reported.<sup>18-20, 25-29, 93-95</sup>

Single parents and parents experiencing significant difficulties that threaten family stability have been shown to perceive a child's chronic illness as having a negative impact on the family.<sup>19,25</sup> Greater family cohesion and marital stability avails support to parents. This reduces parental stress and improves their ability to cope with their child's illness.<sup>19,25</sup> Whereas having a first degree family member with a similar illness helped children adapt to their condition the same effect was not observed in parents.<sup>25</sup>

The severity of a child's illness has an impact on parental perceptions of the child's illness and satisfaction with the management of the condition. Parents of children with more severe illness express lower satisfaction levels when

compared to parents of children who required fewer interventions.<sup>18-21,25,28</sup> Parental understanding of the impact of chronic illness on the child and family is also influenced by non illness related factors such as a child's age.<sup>25</sup> Older children were perceived to have been more adversely affected by the onset of epilepsy more than younger children.<sup>25</sup>

Financial adjustment is a major concern among those with epilepsy and provision for the medical and social needs of such children contributes significantly to parental anxiety. These concerns may have an eventual negative influence on parental perception of the impact of the child's illness on the family.<sup>26-28</sup>

Information regarding a patient's chronic illness coupled with good communicative abilities of caregivers have been shown to contribute to positive patient perceptions regarding one's illness and satisfaction with the care provided.<sup>20,28</sup> The need for information was not related to the known duration of the patient's illness but the duration of illness was related to the specific information a patient felt was relevant.<sup>20</sup>

Perceptions of health providers regarding the information needs and education of patients with chronic illnesses and their families is known to differ from that of parents and patients themselves.<sup>21,28,29</sup> Providers tend to be concentrate on educating patients about the condition and expected outcomes while parents were more concerned about how the illness affected them or their child's lifestyle.<sup>21,28</sup> Parental knowledge regarding management interventions is known to influence their perceptions regarding the well being of their children and the effectiveness of these interventions.<sup>28,29</sup>

Parents place high value on information they receive from their health providers but the understanding of information provided is, in turn, partly dependent on one's literacy level.<sup>22-24,28</sup> Health literacy has been described as "the degree to which individuals have the capacity to obtain, process and understand basic health information needed to make appropriate health

decisions.”<sup>96</sup> This capacity is also influenced by factors such as mode of communication and language.<sup>22-24</sup>

Numerous studies have shown that parental understanding of information provided regarding their child’s illness has a significant impact on a child’s health outcomes. Poor parental understanding has been associated with poor child health outcomes.<sup>22,97-100.</sup> Those who provide care for children with chronic illnesses such as TSC, therefore have an obligation to equip themselves with adequate knowledge and to convey information to the parents of these children using the most effective modes of communication in order to enhance long term health outcomes.

University of Cape Town

## **METHODOLOGY**

### **AIM**

To describe the clinical presentation and parental understanding of TSC at Red Cross Children's Hospital.

### **SPECIFIC OBJECTIVES:**

1. To describe the clinical profile and disease evolution of a cohort of children with Tuberous sclerosis complex managed at Red Cross Children's Hospital.
2. To describe findings of specific investigations performed as part of diagnosis and management of TSC.
3. To describe parental knowledge and perceptions regarding TSC.
4. To determine the effect provision of educational material has on parental understanding of TSC.

### **METHODS**

To fulfil the above objectives two studies were carried out.

#### **A. PATIENT STUDY**

Study design

A retrospective case note review

Subjects

All patients with a confirmed diagnosis of TSC who had been enrolled at the Red Cross Children's Hospital TSC service from January 1996 to December 2008 were eligible for inclusion into the study. All patients that had complete identification data and clinical review notes were included. All patients with incomplete data were excluded.

Measures

Data were captured using a standardized form (Appendix 1) and eventually entered onto an Excel Microsoft word® data sheet.

### Demographic data

These included age, gender, ancestry and the anthropometric measures of height, weight and head circumference. A family history of seizures and or TSC was obtained as part of the background information. Ancestry as a demographic variable was recorded according to the Red Cross standard coding system which classifies patients into broad categories of African, Caucasian, Asian, mixed or other with an inclusion of the patient's home language. The official languages recorded are Xhosa, Afrikaans and English with the rest denoted as other as these are the main languages spoken in this part of South Africa.<sup>101</sup> An indicator of the patients social-economic background was obtained from the Red Cross hospital family income classification coding system. This code is included in the patient's identification details.<sup>102</sup>

### Clinical features

The diagnostic features of TSC that were recorded in patients medical records were classified as either major or minor features and a note made of the age at which they were first observed. Known conditions associated with TSC that were recorded in the folders were identified and recorded. These features included seizures, developmental delay, behavioural disorders, cardiac, and renal manifestations.

Among patients with seizures, the age at onset, details of type and frequency of seizures were recorded. It is standard practice to have formal neuro-developmental assessments for TSC patients in the pre-school age bracket at Red Cross Children's Hospital. Details of these assessments were recorded. Where behavioural disorders were diagnosed, the formal behaviour clinic assessment outcome was recorded. Identified conditions associated with TSC that occurred in body systems other than the central nervous system were recorded when present. An ophthalmologist's examination findings regarding visual function was also recorded.

Interventions used for children with complications of TSC were recorded onto the proforma. Care dependency grants are provided by the government to

parents of children with severe disabilities. We recorded the proportion of children attending the TSC clinic who received these grants.

#### Ethical considerations

The protocol was submitted to the Red Cross Hospital Research Ethics Committee and to the University of Cape Town Committee for Human Research Ethics for review. Approval to conduct the study was granted. This being a review of data in patient folders, consent was not required. Data collected remained confidential and was not used in any way that allowed patient identification. This study adhered to the declaration of Helsinki of 2000.

#### B: PARENTAL STUDY

##### Study design

A prospective observational study

##### Subjects

One parent / legal guardian of each of the children with confirmed TSC and currently attending the service was eligible. Parents who withheld their consent to participate in the study were excluded. Failure in consistency of carer, where a different person attended with the child at each visit also led to exclusion.

##### Data collection procedure.

Prior to the start of the study an extensive literature search did not provide a suitable questionnaire that could be used to determine the level of knowledge parents have regarding TSC in children. A questionnaire (Appendix 3) was designed to determine the baseline knowledge that parents had regarding TSC. Possible responses to structured questions were included while some questions were open-ended. A score was of 0 to 4 was allocated to responses given to the structured questions. This score was not shown to parents during the data collection. A score of 0 was allocated for a wrong response while a score of four was allocated to a complete, correct response.

Prior to the start of the study, each patient currently attending the TSC service was assigned a number from a table of random numbers. The patient group was then divided into two groups by random assignment. Changes in parental understanding of TSC were assessed during two clinic visits that were three months apart. Parents of children in the first group received an information leaflet on TSC after the first visit during the study period while parents in the second group received the information leaflet after the second visit. An adapted version of a parent information leaflet compiled by the TSC alliance was used to provide information to the parents. (Appendix 2).

Questions that sought to establish the parental level of knowledge were based on the information in the leaflet provided. (Appendix 2) During questionnaire design, the use of phrases found in the information leaflet was avoided as much as possible to reduce chances of answers based on pattern recognition.

Consent to participate in the study was obtained during routine, scheduled clinic visits while parents / legal guardians of children with TSC waited for the doctor to attend to them. Verbal explanation regarding the study was given. Following the explanation, written information was provided and read through with the parent to ensure understanding. (Appendix 3) All parents attending the TSC clinic during the course of the study understood spoken English. Written Xhosa and Afrikaans translations of the consent document and information leaflets were requested and provided for three of the parents.

After the parent / legal guardian were satisfied with the information provided written consent was obtained. (Appendix 4) It was emphasized that participation in the study was voluntary and failure to participate would not affect their child's standard of care in any way. Parents and guardians were informed of their freedom to withdraw from the study at any time and of the availability of the investigators to attend to any queries that they had. An interpreter was required on three occasions to interpret the questions into Afrikaans on one occasion and into Xhosa on two occasions.

During the second clinic visit, other sources of information accessed in the interim by parents in both groups were recorded. Important knowledge gaps identified among the carers were addressed during the second clinic visit.

## Measures

### Demographic data

The demographic aspects of the parents that were recorded included age, gender, marital status, educational level, relationship to the child and ancestry. The duration of clinic attendance was determined by recording the age at which the child first presented to the TSC service and the child's current age.

### Parental level of knowledge

Questions whose aim was to establish parental knowledge regarding TSC explored aspects such as diagnosis, aetiology, presentation and management. The first question sought an answer regarding the condition the child was on treatment for. This question was included in order to elicit whether parents understood that all symptoms observed were as a result of TSC.

### Parental perceptions of TSC

Questions that sought to elicit parental perceptions regarding TSC revolved around their views on the impact TSC had on their own children's lives, their major concerns regarding their child's illness and the value of the TSC service to them and their families.

### Ethical considerations

The study protocol was submitted to the Red Cross Hospital Research Ethics Committee and to the University of Cape Town Committee for Human Research Ethics for review. Approval to conduct the study was granted. Parental consent was sought by verbal explanation and provision of written information regarding the study. Where necessary interpretation into the parent's desired language was done for both the verbal explanation and

written information. It was ensured that parents understood what the study involved before written consent was sought from them. They were informed that their participation in the study was totally voluntary and non participation would not in any way alter the care their children received. They were also informed the data would be kept confidential and not used in any way that allowed identification of an individual parent. At the end of the study all parents had received an information leaflet on TSC. This study also adhered to the declaration of Helsinki of 2000.

### **STUDY SITE**

Red Cross Children's Hospital is a government funded health facility located in the Western Cape Province of South Africa. It is a tertiary referral centre for the region. This province is inhabited by approximately 4.8 million people, 1.7 million of whom are children aged 0 to 19 years. Approximately 23.7% of the population of the Western Cape Province is composed of people of African ancestry. Those of mixed descent comprise approximately 53.3% of this population, while the proportion of those of Caucasian descent is estimated to be 19.3%.<sup>103</sup>

A tiered hospital bills system operates at Red Cross Children's Hospital where charges for services are based on the combined family income. To this end patients are categorized from H0 to H3. Those in H0 group having no income and would usually qualify for government social grants. Families in H1 group have a combined family income of less than 50,000 Rand per annum while those in H2 category earn between 50,000 and 100,000 Rand per annum. Families in the H3 category earn more than 100,000 rand per annum.<sup>102</sup>

Patients from families in the H0 category and children below six years of age do not pay for services received at the hospital. Those in H1 class pay a flat rate of 35 Rand for a day's service while those in H2 and H3 classes pay 50% and 100% of the patient fee rate respectively.<sup>102</sup>

## STATISTICAL ANALYSIS

Normally-distributed data were summarised using mean (standard deviation, S.D), otherwise the median (interquartile range, IQR) was used. These results were presented in the form of charts and tables as applicable. Data were analysed using the  $\chi^2$  test, T-test, ANOVA test, Mann-Whitney U test, Wilcoxon paired test, or Kruskal Wallis test, whenever appropriate. Univariate and multi-variate models were fitted to determine strength of associations between exploratory variables and outcomes.

All tests were two-sided. A p-value <0.05 was considered significant. Data were analyzed using the SPSS statistical package for social sciences™ Version 17.

The statistical analyses performed included exploring the relationship between parental baseline level of knowledge and variables such as gender, age, marital status, educational level, ancestry, access to additional sources of information and duration of clinic attendance. An exploration for relationships between a change in the parental level of knowledge following administration of the information leaflet and the same variables was also included.

Factors associated with parental perceptions regarding TSC were assessed by determining the relationship between the mean level of knowledge score of parents who gave specific responses and duration of clinic attendance, change in the level of knowledge and the value of the clinic visits.

## RESULTS

### 1. Patient Demographic data

A total of 41 patient folders were registered into the TSC service from its inception. From these, 34 folders were available for analysis. Three of the available folders were excluded from the study due to incomplete data, leaving 31 for inclusion into the study.

Children of African descent (12) accounted for 38.7% of the cohort while those of mixed descent (19) accounted for 61.3%. On evaluation of the complete case notes only 23 (74.1%) patients were currently attending the TSC service. Five (16.1%) had been transferred out to other services while three (9.6%) were lost to follow up.

Age at presentation at the TSC clinic ranged from 2 to 156 months with a median of 36 (IQR 76.00) months. The patient age at the time of data collection ranged from 8 to 240 months, with a median of 132 months (IQR 96.00).

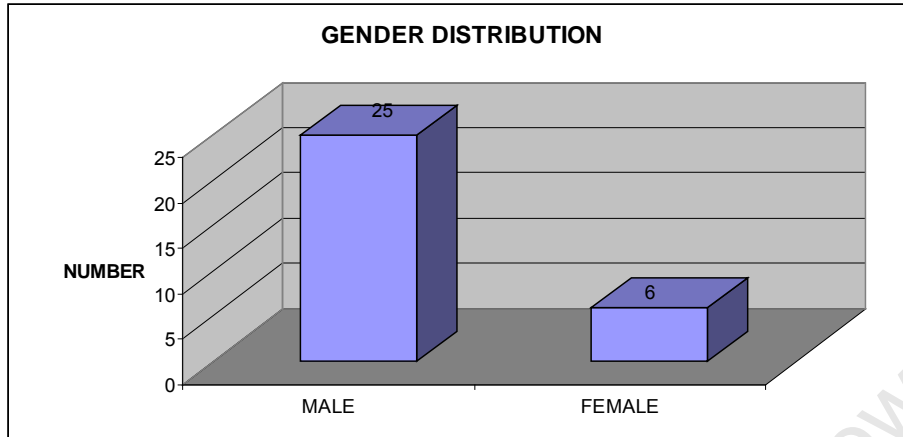
Presentation before one year of age was recorded in 10 (32.3%) cases, before the fifth birthday in 19 (61.2%) cases while the rest 2 (6.4%) presented after 5 years.

The current body weight recorded ranged from 7.8 kg to 90 kg. The median body weight at the latest clinic visit for this cohort of children was 34 kg (IQR 28.00). The height ranged from 170 to 68 cm. The median height was 134 cm (IQR 35.00).

In this cohort nine (29%) patients were classified in economic class H0 while 16 (51.6%) were placed in class H1. Six families were classified as economic class H2 or H3 accounted for 19.3% of the cohort. At least half of the cohort 16 (51.6%) children received monthly care dependency grants.

As shown in Figure 1 below, there were 25 (80.6%) males and 6 (19.4%) females in this cohort. The male: female ratio was 4:1.

Figure 1: Gender distribution of children with TSC



## 2. Clinical manifestations and management

A median of three major characteristics (IQR 4.00) of TSC were recorded for each child with a range of one to seven major characteristics. Minor features were recorded in only eight patients with a median of one minor characteristic per patient. Figure 2 below shows the frequency of occurrence of specific major features of TSC.

Figure 2: Frequency of Major features of Tuberous Sclerosis.

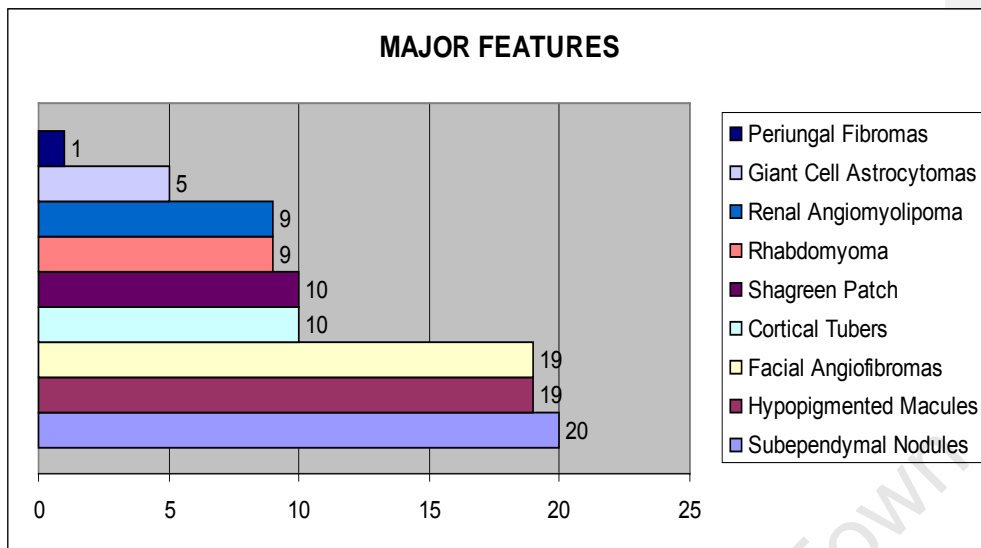
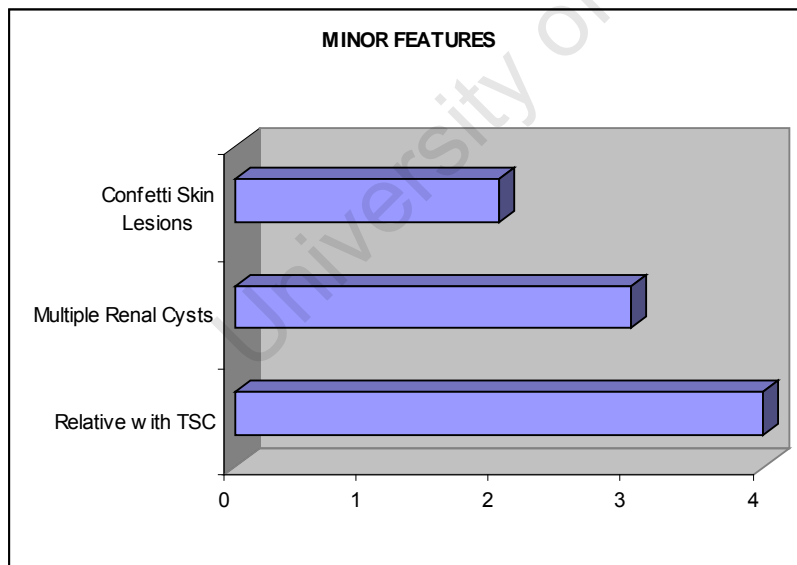


Figure 3 below summarizes the frequency of minor features of TSC recorded in the Red Cross Hospital cohort.

Figure 3: Frequency of Minor features of Tuberous Sclerosis Complex.



A positive family history of seizures was reported by eight (25%) cases in this cohort, although only four (12.9%) children had a positive family history of TSC.

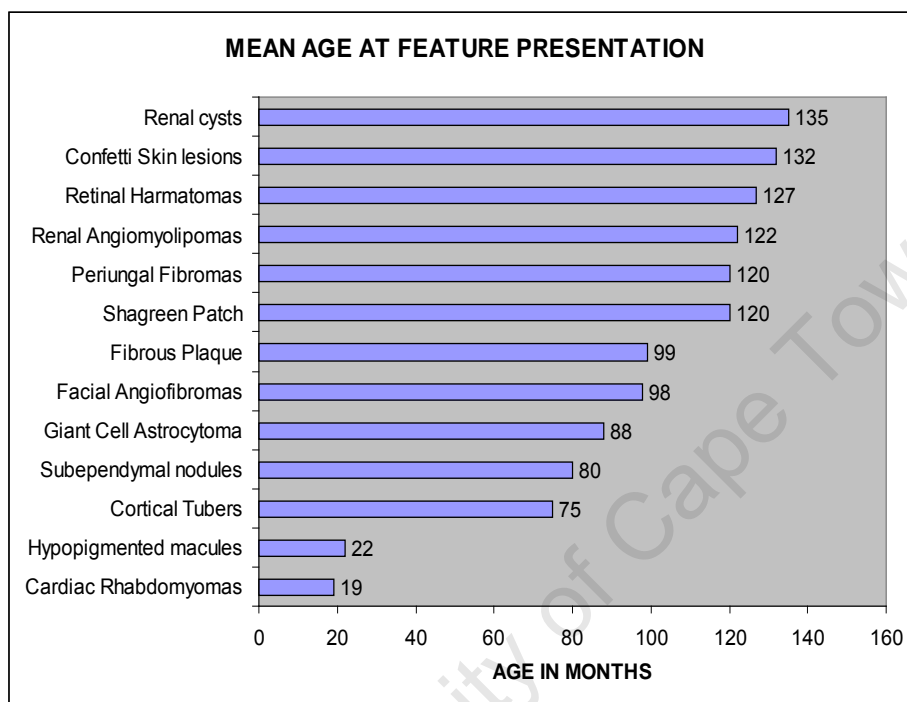
Table 1 below shows the proportions of patients with specific features of TSC in this cohort.

Table 1: The Frequency of specific features of TSC observed in this cohort.

Feature of Tuberous Sclerosis	Frequency	Proportion of cohort (%)
Facial Angiofibromas	19	61
Hypopigmented Macules	19	61
Shagreen Patch	10	32.2
Fibrous Plaque	9	29.0
Cortical tubers	10	32.2
Subependymal nodules	20	64.5
Giant cell astrocytomas	5	16.1
Retinal Hamartomas	3	9.6
Cardiac Rhabdomyomas	9	29.0
Renal Angiomyolipomas	9	29.0
Periungual fibromas	1	3.2
Relative with TSC	4	12.9
Retinal achromic patch	1	3.2
Confetti skin lesions	2	6.4
Multiple renal cysts	2	6.4

Figure 4 below illustrates the mean ages at which features of Tuberous sclerosis were recorded.

Figure 4: Mean patient age at feature presentation.



In this cohort of children with TSC, a total of 11 (35.5%) children had renal manifestations of TSC. Two (6.4%) of these children had symptoms related to their renal complications, with complaints of right flank pain in one child and haematuria in the other. Clinical manifestations of cardiac involvement were recorded in one patient (3.2%) who had arrhythmia.

Ophthalmology evaluations were performed on 24 (77.4%) children in this cohort. Among these, four children (16.7%) had abnormal findings on fundoscopy. Three patients (12.5%) had mulberry-type retinal hamartomas and one also had retinal hypoplasia. The fourth (4.2%) patient had a semi transparent retinal hamartoma and hypopigmented spots on his iris.

Seizures were observed in 27 patients (87.1%). Infantile spasms were reported in three (11.1%) of these patients, while partial seizures occurred in 11 (40.7%) of the patients with seizures. Generalized seizures were reported in 15 (55.5%) of patients with seizures. Two (7.4%) patients had more than one seizure type, where one presented with infantile spasms that later evolved into generalized tonic clonic type. The other had focal seizures as well as generalized tonic clonic seizures. The median age at onset of seizures was 9 months, IQR 14.01 (range 2 to 135 months). Guardians of seven of the 27 patients (25.9%) were themselves known to have seizure disorders while one patient had a paternal grandfather with seizures.

Good seizure control (no seizures) was reported for 16 (59.3%) patients. Eleven (40.7%) of the children with seizures were reported as having a seizure frequency that ranged from three times per week to once a month.

Among those with ongoing seizures two (7.4%) were on one anticonvulsant, four (14.8%) patients were on two anticonvulsants while five (18.5%) patients were on three anticonvulsants.

As shown in the Figure 5 below, 20 (74.1%) of the children with seizures received sodium valproate while 11 (40.7%) received clobazam. In addition, 10 (37.0%) of these children received carbamazepine, four (14.8%) received lamotrigine while topiramate, clonazepam and phenytoin were all prescribed to one child only. More than one anticonvulsant was required in 15 (55.5%) of the 27 patients with seizures.

Figure 5: Frequency of Anticonvulsant use.

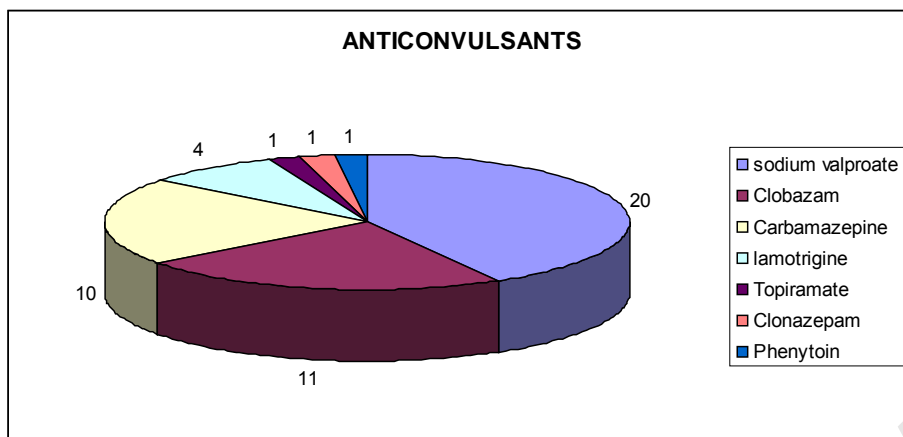


Table 2 below shows the distribution of anticonvulsant use according to the seizure type.

Table 2: The Distribution of anticonvulsant use according to the type of seizure.

Anticonvulsant	Infantile seizures (3 patients)	Other generalized seizures (15 patients)	Partial Seizures (11 patients)	Total
Sodium Valproate	3	14	3	20
Clobazam	2	6	3	11
Carbamazepine	0	2	8	10
Lamotrigine	0	4	0	4
Others	1			1

(Note: Two children had more than one seizure type. Total number who had seizures was 27)

None of the children had received epilepsy brain surgery, a vagal nerve stimulator or the ketogenic diet for seizure control.

Neuro-developmental assessments were carried out on 26 (83.8%) patients. Fourteen (53.8%) of those assessed were found to have global developmental delay (median DQ score 50.4, IQR 10.4). Two (7.7%) of those assessed had delayed fine motor development and one (3.8%) had delayed speech development. Normal neuro-developmental assessments were recorded for 9 (34.6%) (mean DQ 92 SD 3.5) of those who had an assessment done.

School placement data indicated 13 (41.9%) children in this cohort attended a mainstream school while seven (22.5%) were placed in a remedial class. Among the rest, three children (9.6%) attended a training school, three others (9.6%) attended a special care center and five families (16.1%) chose to keep their children at home.

Behavioural disorders were not a concern amongst 19 (61.3%) children. Following behaviour clinic assessments, two children (6.4%) were found to be both hyperactive and aggressive, while six (19.3%) were considered hyperactive. Aggressive behaviour was observed in four (12.9%) other children but none of the children were thought to be depressed or to suffer from anxiety.

One of the children who was both aggressive and hyperactive received risperidone as well as sodium valproate, clobazam and carbamazepine for his seizure disorder while the other was only on sodium valproate and carbamazepine.

Neuro-psychiatric disorders were recognized in four (12.9%) children. A diagnosis of oppositional defiant disorder was made in two (6.4%) children while one (3.2%) child had autism and another (3.2%) had conduct disorder.

### 3. Investigations

As shown in Table 2 below, electroencephalograms (EEG) and computer tomography (CT) scans were the most frequent investigations performed in this cohort of patients.

The frequencies of abnormal results detected by abdominal ultrasound, echocardiogram, CT scan and MRI of the brain have been summarized in Table 3.

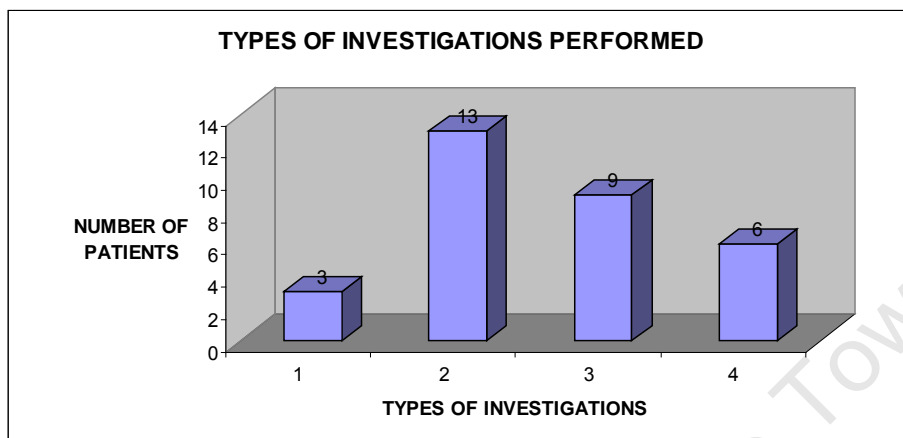
Table 3. Frequency and results of investigations performed.

Investigation	Frequency		Abnormal results	
	No.	%	No.	%
Electroencephalogram (EEG)	22	70.9	11	50.0
CT Brain	23	74.2	23	100.0
Abdominal Ultrasound	21	67.7	11	52.4
MRI Brain	10	32.2	10	100.0
Echocardiogram	10	32.2	5	50.0
Electrocardiogram (ECG)	2	6.4	1	50.0

Eleven (50%) of the 22 EEG's performed were abnormal. Five (45.5%) of the abnormal EEG's showed focal discharges, three (27.3%) of the abnormal EEG's had generalized spike and wave discharges and two (18.2%) showed generalized slowing. Two ECG'S were performed one of which detected multiple ectopic beats.

As shown in the figure 6 below, 28 (90.3%) of the patients had at least two types of investigations performed while 15 (48.4%) patients had at least three different types of investigations performed.

Figure 6: Frequency of investigations performed.



#### 4. Parental demographic profile

A total of 23 children currently attend the TSC clinic at Red Cross Children's Hospital. Parents of 21 (91.3%) patients gave consent to participate in the study, 18 (85.7%) were female and three (14.3%) were male.

The parental group had a median age of 38 years (IQR 10.5) with a range from 31 to 55 years. There were 14 (66.7%) married parents, Four (19.0%) were single and three (14.3%) were separated from their spouses. There were 14 (66.7%) parents of mixed descent and seven (33.3%) of African descent.

All parents with the exception of one (4.7%) had received formal schooling while seven (33.3%) had attained a primary level of education. Secondary education was attained by ten parents (47.6%) and three (14.3%) had received tertiary education.

The mean duration of attendance at the TSC service for this group of parents was 86.19 months (SD 56.1) and ranged from 5 to 190 months.

Baseline parental characteristics of those who had received a leaflet were compared with those of parents who did not receive an information leaflet. No statistically significant differences were detected. These findings are summarised in Table 4 below.

Table 4: Comparison of parental background characteristics based on information leaflet distribution.

Variable	Received Leaflet No: 11	Did not receive Leaflet No: 10	p Value
Mean Age (yrs)	39.00	41.3	0.41
Gender No: (F) (M)	10 1	8 2	0.47
Marital status No: (married) (not married)	5 6	9 1	0.06
Mean educational level (grade 8) No:	7	6	0.28
Mean duration of clinic attendance (months)	92.09	79.70	0.62
Ancestry (mixed) (African)	7 4	7 3	0.75

## 5. Parental knowledge of TSC

The first question that was administered, sought to explore if parents knew the condition for which their child was on treatment. Thirteen (61.9%) parents knew that their child had TSC while eight (38.1%) did not know.

Two (9.5%) parents knew that TSC could be inherited and could also occur spontaneously while seven (33.3%) parents knew TSC was a heritable condition. A total of 12 (57.1%) parents did not know the cause of TSC.

Twelve parents (57.1%) knew that a diagnosis of TSC was made by full clinical evaluation and investigations while four (19.0%) parents stated that a diagnosis of TSC could be made by physical examination. Five (23.8%) parents did not know how a diagnosis of TSC was made.

Parental responses at the start of the study to the question that sought to establish which investigations they knew could be done to make a diagnosis of TSC are summarised in Tables 5 and 6 below.

Table 5: The number of investigations for TSC known to parents.

Number of investigations stated	Number of parents	Proportion (%)
1	9	42.9
2	7	33.3
3	2	9.5
4	3	14.3
Total	21	100

Table 6 below shows the actual types of investigations that parents of children with TSC knew.

Table 6: Types of investigations for TSC known to parents.

Investigation	Number of Parents	%
MRI Brain /CT Brain	13	61.9
Renal ultrasound	8	38.1
Echocardiogram	2	9.5
EEG	10	47.6
Wood's Lamp	0	0

Parental understanding of TSC manifestations was sought by asking them what organs or body systems were affected by TSC. The brain, skin, kidney, heart and eyes were all identified as organs affected by TSC. Responses to this question are summarized in Table 7 below.

Table 7: Number of body organs parents knew could be affected by TSC.

Number of body organs	Number of parents	Proportion (%)
1	8	38.1
2	5	23.8
3	5	23.8
4	3	14.3
Total	21	100

That TSC is not a curable condition was known to 13 (61.9%) parents while 5 (23.8%) thought it was curable. Three (14.3%) parents did not know whether it was curable or not.

Five (23.8%) parents responded that there was nothing that could be done to help children with TSC live better with their condition while six (28.5%) parents stated giving medication was of benefit to children with TSC. Three (14.3%) parents felt that either giving medications or visiting the doctor were adequate interventions. Seven parents (33.3%) knew that giving medications and visiting the doctor to address the current problems and evaluate for new complications were suitable interventions.

In response to a question that requested parents to list any problems that could be observed in children with TSC, all except one parent included seizures in their responses. This particular parent stated there were no complications observed in these children as her one year old had cardiac rhabdomyomas that resolved at three months of age and his cortical tubers had not caused him any problems.

Table 8 below summarizes the complications of TSC identified by parents.

Table 8: Complications of TSC known to parents of children with TSC

Complication Identified	No.	%
Seizures	20	95.2
Behavioural problems	6	28.6
Learning difficulties	7	33.3
Inability to participate in school activities	4	19.0
Inability to participate in social activities	3	14.3

A score was assigned to answers given in response to questions that sought to establish the level of parental knowledge. The median score for the whole group of parents at the start of the study was 30 out of a possible total score of 87 points. The scores ranged from 16 points to 71 points, with a median score of 32.60 (IQR 29.0).

Following the first visit 11 (52%) parents were given information leaflets to take home. (Appendix 2) On a subsequent visit, the same questionnaire was administered and a score assigned to the answers. The median score for the whole group on the second visit was 42 points (IQR 38.00). The median percentage change in the total scores for the whole group was 4.6% (IQR 19.45).

Table 9 below compares the recorded scores of parents who received information leaflets with those of parents who did not receive leaflets.

Table 9: Change in parental level of knowledge following leaflet administration

Variable	Group of parents who Received Leaflet	Group of parents who did not receive leaflet	p value
Baseline Mean Score	34.2	39.2	0.97
Second visit Mean score	51.7	41.8	0.02
Change in level of knowledge	20.1%	2.9%	0.001

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A statistically significant difference: p value =0.001, was observed in the change in the level of knowledge on comparison between the parent group that received a leaflet and the group that did not.

No statistically significant associations were observed between parental age, gender, marital status, ancestry or duration of a child's illness and the level of knowledge either at the beginning of the study or at the subsequent visit. These findings are summarised in Table 10 below.

Table 10: Factors associated with level of knowledge at baseline and second stage of study.

Variable	Association with initial score (p value)	Association with % change in score (p value)
Parental age	0.31	0.95
Parental gender	0.13	0.52
Parental Marital status	0.71	0.22
Parental Ancestry	0.92	0.75
Known duration of child's illness	0.37	0.63

A higher parental level of education had a positive association with an increase in the level of knowledge. Exploration for significance in changes in the level of knowledge was performed for the group as a whole and also based on the mean educational levels for the group. These findings are summarised in Table 11 below.

Table 11: Association between the parental level of education and change in level of knowledge

Variable	Association with baseline score (p value)	Association with % change in knowledge score
Parental education	0.01	0.02
Mean parental level of education (grade 8)	0.045	0.003

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All parents cited the TSC service as their main source of knowledge regarding their child's illness. Four (19.0%) parents indicated having received additional information from other clinical services within and outside of Red Cross Children's Hospital and the internet. The difference in baseline knowledge score for this group of parent had no statistically significant difference when compared to that of parents who had no other source of information. [p value = 0.76]

During the second visit we sought to establish if parents had accessed other sources of information other than that provided by the TSC service. Seven (33.3% %) parents had obtained information from other sources but the change in the level of knowledge in those who did compared to those who had no access to other sources of information on TSC was not statistically significant [ p value = 0.24].

#### **6. Parental perceptions of TSC**

In response to a question that sought to establish the perceived extent to which parents felt TSC had affected the quality of their children's lives, 13 (61.9%) of parents felt the condition had had a significant negative impact on their children. Three (14.3%) Parents felt that TSC had a moderate negative impact on the quality of their children's lives while five (23.8%) felt TSC had not had any effect on the quality of their children's lives.

The mean baseline knowledge score for the parents who felt TSC had a major negative effect on their children was 37.5 (SD 15.6), that of those who felt the effect was moderate was 29 (SD 14.0) and that of those who felt TSC had had no effect was 41.2 (SD 21.2). The difference in the mean baseline knowledge scores of these three groups of parents was not statistically significant. [p value = 0.61]

The change in the mean parental level of knowledge when the first and the second visit scores were compared had no statistically significant association with parental perception of the impact of TSC. [p value = 0.59] These findings are summarised in Table 12 below.

Table 12: Parental perception of the impact of TSC on their child's quality of life

Parental perception of TSC impact	First visit		Mean baseline score	Second visit		Mean second score
	No.	(%)		No.	%	
Major impact	13	61.9	37.5	16	76.2	45.3
Some impact	3	14.3	29	1	4.8	68
No impact	5	23.8	41.2	4	19.0	48.2
Total	21	100.0		21	100.0	

An assessment for association between the duration of a parent's clinic attendance (as indicated by the known duration of a child's illness) and an individual parent's perception of the value of the clinic visit showed no statistically significant difference between those who felt it was useful compared to those who felt it was not useful. [p value = 0.13]

Similarly, there was no statistically significant difference in the baseline level of knowledge between those who felt that visits to the clinic were useful compared to those who felt it was of no value. [p value = 0.81]

Two (9.5%) parents at the beginning of the study felt that clinic visits had not been of much benefit to their children. The reason given by both of them was that their children had severe behavioural problems and this aspect had not significantly improved despite repeated visits.

During the second visit only one (4.7%) parent perceived visits to the clinic to be of no benefit to her child to the lack of change in the child's aggressive behaviour. Both parents had received an information leaflet.

Table 13 below summarises the issues that were of greatest concern to parents of children with TSC.

The table also shows there were no statistically significant differences in the baseline level of knowledge and in the level of knowledge at the second visit on comparison between parents who raised a specific concern and those who did not.

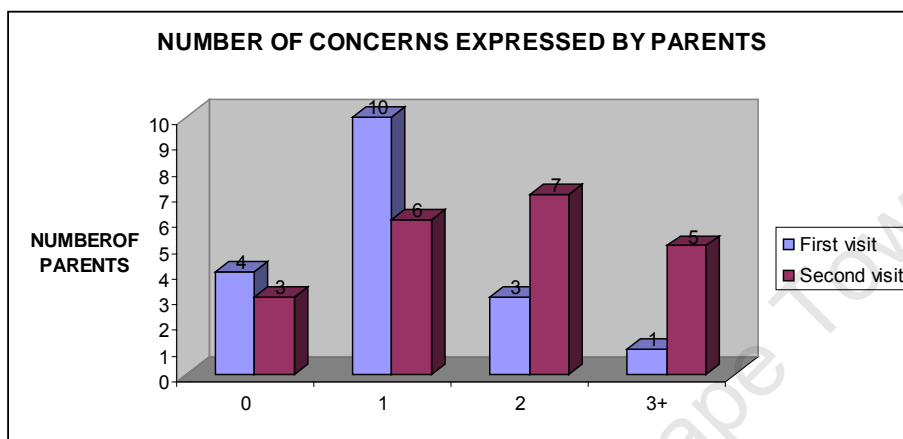
Table 13: Issues of concern to parents regarding TSC

Issue of concern	First Visit No. %	Mean baseline score	p value	Second Visit No. %	Mean second score	p value
Severity of illness	4 19.0	39.2	0.30	10 47.6	44.0	0.34
An uncertain future	12 57.1	40.3	0.82	18 85.7	48.6	0.18
Effect of the child's illness on the family	4 19.0	32.7	0.15	7 33.3	42.7	0.44
Effect of the child's illness on me as a caregiver	0 0	0	0	3 14.3	32	0.18
Cost of care / medication	0	0	0	0	0	0

At the first visit, 10 (47.6%) parents expressed concerns regarding only one of the major issues listed above. Three (14.3%) parents were worried about two specific issues while one (4.8%) parent was concerned about three issues. Four (19.0%) parents had no major concerns.

At the second visit, six (28.6%) parents cited one major issue of concern regarding their child while seven (33.3%) parents cited two major issues of concern. Five (23.8%) parents worried about three or more aspects of the condition while three (14.2%) parents had no major concerns. These findings are summarized in Figure 7 below.

Figure 7: Number of concerns expressed by parents



There was no statistically significant difference in the total number of major concerns expressed when those who received a leaflet were compared to those who did not receive one. These findings are summarised in Table 14 below.

Table 14: Comparison of the number of major concerns between parents who received a leaflet and those who did not receive one

Total number of concerns expressed	Received information leaflet	Did not receive information leaflet	P value
First visit	14	8	0.91
Second visit	20	17	0.75

## **DISCUSSION**

### **Patient Clinical profile**

The Western Cape Province is inhabited by three major ancestral groups.<sup>103</sup> The ancestral distribution of patients in this cohort does not mirror that of the inhabitant population as only the mixed and African ancestry groups are represented. This discrepancy may be due to the fact that Red Cross Children's Hospital being a government facility is frequented by the lower income groups of the population. This observation is supported by the facts that majority (80.6%) of the patients in our cohort came from families in the H0 and H1 categories, and over half (51.6%) of the families in this cohort received government income subsidies in the form of care dependency grants.

Whereas a clear male predominance with a male to female ratio of 4:1 is noted in our data, this is not a uniform finding with some of the other studies reporting a higher frequency of female children.<sup>4,104</sup>

A positive family history of Tuberous Sclerosis was recorded in only four (12.9%) of our patients. This finding is not unexpected as other studies also indicate that a family history of TSC is uncommon because at least two thirds of tuberous sclerosis patients have spontaneous mutations.<sup>1, 4-7</sup>

All children in this cohort had definite TSC as they all fulfilled the diagnostic criteria that require presence of two major features.<sup>1-4,8,48</sup> This is a useful finding in our context as genetic testing is neither available in South Africa nor fully reliable as only 60 to 80% of those who fulfill the diagnostic criteria have detectable mutations.<sup>11,23,24</sup> Two to ten percent of people who carry the TSC gene are not detected by genetic testing due to mosaicism.<sup>7</sup>

More than half of the children in our cohort had a diagnosis of TSC made before five years of age. This is in keeping with data from other studies that estimate the average age at diagnosis for children with tuberous sclerosis to be five years.<sup>4,11</sup> However, this trend is changing with the increasing use of

prenatal ultrasound and diagnostic testing.<sup>4,8,11</sup> That none of the children in our cohort had a prenatal diagnosis of Tuberous Sclerosis may be due to the previously low level of availability and utilization of prenatal ultrasound evaluation in South Africa.

Hypopigmented macules have been reported in about 90% of children with TSC and usually appear in early infancy.<sup>1,2,4,8,63,66</sup> Less than two thirds of the children in this cohort had this condition. This may be due to the fact that none of them had a wood's lamp examination done as this would probably have identified more cases of hypopigmented macules. Hypopigmented macules had a mean presentation age of 22 months. The later presentation of this feature in our cohort could be related to the overall mean age of diagnosis of five years by which time guardians are likely to be unsure of the time when macules were initially noted.

Facial angiofibromas usually appear by five years of age as small papules in the malar region. They increase in size and number becoming prominent by adolescence.<sup>1,2,8,12,37,48,63,66</sup> The recorded mean presentation age of 8 years for facial angiofibromas in the Red Cross cohort most probably represents the age at which the lesions became prominent and caused cosmetic related concerns to the parents rather than the actual time of appearance.<sup>37</sup>

The median age of this cohort at the time of the study was 11 years and the recorded frequency of facial angiofibromas was 61%. Facial angiofibromas are usually observed in at least three quarters of children with TSC.<sup>1,2,8,12,37,51,64,67</sup> It is possible that the proportion of those with facial adenofibromas in our cohort was under-reported hence accounting for the lower proportion. An alternative explanation could be that children with TSC in this part of the world have a slower onset and progression of facial angiofibromas.

Confetti lesions were recorded in only two patients and the age of presentation was recorded for only one patient (11years). This finding may not reliably reflect the age at presentation of confetti lesions in this cohort as they

are known to appear much earlier and are present at birth in some cases.

<sup>1,2,8,12,37,48,63,66</sup>

Shagreen patches and periungual fibromas are lesions typically seen in about a third of adolescents with tuberous sclerosis. <sup>1,2,8,12,37,48,63,66</sup> A reported mean age of 10 years at presentation as noted in our cohort would be in keeping with findings from other studies. <sup>1,2,48</sup> The incidence of retinal hamartomas ranges from 4 to 76 % with an increasing incidence observed with increasing age. <sup>8,102</sup> The mean age at detection in this cohort was 10.5 years at which age the incidence is estimated to be 17.2%. <sup>8</sup> The reported incidence of 16.7% is in keeping with findings from other studies.

Cardiac rhabdomyomas had a mean presentation age of 19 months in the Red Cross Children's Hospital cohort. Cardiac rhabdomyomas are known to be present at birth hence the later mean age at presentation could be related to the mean age at diagnosis of five years by which time the indication for echocardiogram evaluation in an asymptomatic child was probably low. Cardiac rhabdomyomas are a common feature at initial presentation in infancy with frequencies of 90% reported in some series, and are known to resolve after infancy. <sup>1,2,4,8,11,48,61,89</sup> The low frequency of cardiac rhabdomyomas (29%) could also be related to the low rate of echocardiogram evaluation (29%).

Cortical tubers and subependymal nodules have been detected on prenatal imaging and before age two months postnatally. <sup>1,4,8,104</sup> The mean age at detection of 75 and 80 months respectively for these two lesions in this cohort most likely correlates with the time at which neuroimaging occurred and not the actual age at which these abnormalities developed. A mean age of seven years for detection of giant cell astrocytomas is also not in keeping with previous data and this finding may also be related to the later average age at presentation to the service. <sup>1,4,8,104</sup> Low availability of MRI techniques necessary for detection of cortical tubers in our environment could also have contributed to the late age at detection.

Giant cell astrocytomas have been reported in 10% of infants and in 6 to 14% of children with TSC by early childhood.<sup>1,2,4,6,8,48</sup> The frequency of Subependymal giant cell astrocytomas in the Red Cross Children's Hospital cohort (16.1%) is similar to that reported in other studies.<sup>1,2,4,6, 8, 48.</sup>

In a previous study, Magnetic resonance imaging (MRI) of the brain in infants showed cortical tubers and subependymal nodules in 93% and 88% respectively.<sup>4</sup> In the Red Cross Children's Hospital cohort, subependymal nodules were reported in almost two thirds of the patients (64.5%) while cortical tubers had a frequency of 32.2%. These frequencies of subependymal nodules and cortical tubers correlate closely with the frequencies of CT scan Brain (74.2%) and MRI brain studies (32.2%) performed on this cohort. This observation can be explained by the fact that calcified subependymal nodules are adequately detected by Computer tomography (CT) scan of the brain while cortical tubers are better detected by MRI brain studies.

Renal angiomyolipomas occur in 70% to 80% of children older than 10 years who have TSC.<sup>2,48,89</sup> The mean age at detection of renal angiomyolipomas in our study was 10 years. This finding was reported in only 9 (29%) of these children though an abdominal ultrasound was performed on 21 (67.7%) children. It is therefore plausible that the rate of angiomyolipoma development in South African children with TSC differs from that in other populations. However it is difficult to draw firm inferences due the small numbers of children detected to have angiomyolipomas.

Symptoms arising from the presence of renal angiomyolipomas are rarely observed before the third decade of life and tend to be observed in adolescents and adults.<sup>8</sup> The two children with angiomyolipomas who were symptomatic in this cohort were aged 14 and 16 years, which is in keeping with findings from previous studies.

Seizures are a common presenting feature in infancy and overall 80% to 90% of all children with TSC develop epilepsy.<sup>1-4, 6-11,13</sup> The frequency of 87.1% that was observed in this review, therefore matches that reported in other

studies. The range of age of onset is also unremarkable and in keeping with that reported in other studies. Intractable seizures occurred in nine (33.3%) of those with seizures. It is a well recognized fact that intractable seizures are common in children with TSC but the estimated prevalence is not well defined in literature.<sup>6,30,37,71</sup>

Sodium valproate which is recommended for generalized epilepsies was the most commonly prescribed anticonvulsant with a 64% utilization rate. This was appropriate therapy as generalized and complex seizure disorders were observed in more than half (66.6%) of those with epilepsy in this cohort. Vigabatrin is particularly useful in patients with infantile spasms and TSC.<sup>1,8,37,71</sup> It is notable that despite the fact that three (11.1%) of the patients had infantile spasms none of them received vigabatrin. Two of these three patients are now well controlled and the third has a generalized tonic clonic seizure once or twice a month.

Cortical tubers and other TSC related brain malformations may form foci for partial seizures.<sup>4,6,37,71</sup> Carbamazepine is the anticonvulsant of choice for these form of seizures while clobazam, lamotrigine, and topiramate are added as second line agents if there is suboptimal response to carbamazepine.<sup>1,8,71</sup> These treatment guidelines were followed in the management of partial seizures in the Red Cross cohort. Eleven children had partial seizures, eight of whom were on carbamazepine. Additional anticonvulsants agents were required for seizure management for four of these eight patients.

Early descriptions of TSC by scientists such as Voigt and Bourneville included mental retardation but it is currently known only approximately half of those with TSC have cognitive disabilities.<sup>1-3,6-8,15,16,37</sup> Our results are in keeping with those of other studies as 53% had global developmental delay and 58.1% needed alternative placement as they could not attend a mainstream class.

One patient in our cohort had autism and infantile spasms that evolved into a complex partial seizure disorder that was well controlled. He also had severe global developmental delay and required placement at a special care

institution. It is estimated that the prevalence of autism and pervasive developmental disorders in children with both intellectual disability and TSC is three times greater than that in those without both co-morbidities. Infantile spasms are also considered a risk factor for the development of autism.<sup>14,17</sup>

An Electroencephalogram study (EEG) were performed for 22 (70.9%) children and half of them were reported as abnormal. It is estimated that 75% of all patients with TSC will have abnormalities on EEG, 48% of which have focal and multifocal discharges and 8% have generalized spike and wave abnormalities.<sup>80</sup> Similar findings are noted from our EEG recordings with 45% of abnormal EEG's showing focal discharges. However a higher proportion (27.3%) of generalized spike and wave abnormalities was observed in our study compared to that reported by Gomez.<sup>80</sup>

#### **Assessment of parental level of knowledge.**

The Red Cross Children's Hospital service was the only source of information regarding TSC for majority (83.6%) of the parents interviewed. This fact highlights the importance of providing parents with adequate information in addition to the clinical service on an ongoing basis. From previous studies it is known that patients attach great value to information given by their health providers regarding their condition.<sup>20</sup>

The known duration of illness which equated to the duration of attendance at the clinic had no association with the level of knowledge a parent had at the beginning of the study. This fact may indicate a lack of additional education and reinforcement of an understanding of TSC beyond the initial counseling. Previous studies have demonstrated that patients' need for education regarding their condition does not correlate to the duration for which they have had their condition.<sup>20,21</sup>

More than half of the parents knew that their child was on treatment for TSC and understood how a diagnosis was made. They also knew the complications and manifestations of TSC and the fact that TSC is not a curable condition. However, that the cause of TSC was not as well

understood may be due to the fact that this is a particularly difficult concept for non medically trained people to understand. It has been observed previously that the complexity of a clinical concept may influence the patient's ability to understand the facts presented though this may also be influenced by a health provider's communication skills<sup>22</sup>

One fifth of the parents interviewed felt that there was not much that could be done for patients with TSC. This perception was probably due to the observed chronicity of the condition and persistence of complications in their own children. Indeed, three of the five parents who gave this response had children with intractable seizures and one had a child with a behavioral disorder.

It is important to note that a statistically significant difference in the baseline level of knowledge was not detected between the parents who received an information leaflet when compared to those who were not issued with one at the end of the first clinic visit.

Provision of an information leaflet was associated with a statistically significant difference in the change in parental level of knowledge when those who received a leaflet were compared to those who did not. [p value =0.001] This observation indicates that provision of written information is a useful way of improving parental understanding of their child's condition.

A significantly greater change in the level of knowledge was observed among parents who had attained a secondary school level of education (grade 8). A higher level of education would equip one better with the ability to understand written information and could also be a motivating factor for one to actually read the information provided.<sup>22</sup> Low literacy skills have been shown to positively correlate with poor disease specific knowledge in other studies.<sup>22-24</sup>

The TSC service was the main source of information for this group of parents. Access to other sources of information was limited and did not contribute

significantly to their level of knowledge. This finding as observed in other studies, serves to underscore the importance of provision of education by clinicians who care for patients with chronic conditions such as TSC.<sup>21,22</sup>

### **Parental perceptions regarding TSC**

Parental level of knowledge as indicated by the baseline and second scores had no correlation with parental understanding of the impact of TSC on their child's life. This finding contradicts findings from other studies which suggest that the parental level of knowledge determined the parent's perceptions regarding the child's illness.<sup>29</sup>

It is notable that children of three of the five parents who felt TSC had little or no effect on the quality of the child's life had well controlled seizure disorders while two children had not ever had seizures. None of the five children had pervasive developmental disorders. It is very likely that parental assessment of the effect of TSC on a child was based on parental assessment of the child's functional level and not the actual complications the child had. Rodenburg and Morrow have previously shown that parental perception of a child's illness had a positive correlation to the severity of the child's illness.<sup>19,28</sup>

Two parents (9.5%) felt that the clinic visits had not been useful. One of the children had global developmental delay, attention deficit hyperactivity disorder and an Autistic spectrum disorder. The other child had seizures an oppositional defiant disorder, and aggressive behaviour. These were the only children in the cohort that required risperidone and methylphenidate as part of their management. Behavioural problems in children with complex seizure disorders and learning disabilities are particularly difficult to manage.<sup>18</sup> The complexity of these children's illness may explain why their parents felt clinic visits had not been of much value in changing their child's condition.

Previous studies have indicated financial constraints to be an issue of concern to those with epilepsy.<sup>26,27</sup> Although 87% of the children in this cohort had seizures and required anticonvulsant medications, none of the parents considered the cost of medications or the cost of care of these to children be

a major concern. This finding may be due to the fact that majority (80.6%) of the patients in this group were in H0 and H1 income classes and did not shoulder the full cost of care for these children as they were entitled to free services at the hospital. In addition, half the families (51.6%) receive care dependence grants that helped ease the burden of care imposed by TSC.

A statistically significant difference was not detected in the number of concerns expressed when those who received a leaflet were compared to those who did not receive one during the first visit. The fact that a greater total number of concerns were expressed by both groups at the second visit may indicate a heightened awareness of problems attributable to TSC as a result of participation in this study.

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## **CONCLUSIONS**

A definite diagnosis of TSC can be made for children in South Africa. All children seen at The TSC service at the Red Cross Children's Hospital fulfill the diagnostic criteria for TSC.

The clinical profile of the cohort of children seen at the Red Cross Children's Hospital is similar to that of other cohorts described in literature.

Parental understanding of TSC can be improved by provision of written information for those with at least a grade eight (secondary school) level of education.

Parental understanding of the impact of TSC on their children and their major concerns regarding the condition are not associated with the parental level of knowledge.

The known duration of a child's illness has no correlation with the parental level of knowledge or the parental perception regarding the value of the TSC service to their children.

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## **RECOMMENDATIONS**

- The TSC service at Red Cross Children's Hospital should formally adopt the information leaflet used in this study to help educate parents of children with TSC.
- A significant proportion of parents (42.8%) attending the service have a low level of education and their information needs would not be sufficiently met by provision of an information leaflet. Group education sessions could address this need and clarify difficult concepts regarding TSC.
- Parental education on TSC needs to be continuous throughout the time a child attends the service.
- Parental concerns regarding the future of their children need to be addressed. This can be achieved by holding forums where issues that include training and placement opportunities, adolescent care and alternative carers in the absence of a parent are addressed.

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B) Minor features

Age at presentation

13. Relative with T.S
14. Wedge shaped area of cortical /  
sub cortical calcification
15. Multiple sub cortical hypodense areas
16. Dental pits
17. Hamartomatous rectal polyps
18. Bone cysts
19. Cerebral white matter radial migration lines
20. Gingival fibromas
21. Non renal hamartomas
22. Retinal achromic patch
23. Confetti skin lesions
24. Multiple renal cysts

TOTAL NUMBER

**Other clinical features**

**Age at presentation**

1. Seizure Type
  - a) Infantile spasms
  - b) Generalized Seizures
  - c) Partial seizures
2. Seizure frequency in preceding 3 months
  - / week
  - /month
3. Developmental delay
  - a) Gross motor
  - b) Fine motor
  - c) Language
  - d) Personal Social
  - e) Not formally assessed

4. Behavioural manifestations

- b) Hyperactivity
- c) Aggression
- d) Anxiety
- e) Depression

5. Neuro – Psychiatric co-morbidities

- a) Autism spectrum disorders
- b) Conduct disorders
- c) Oppositional defiant disorder

6. Learning Institution attended: (indicate)

- a) Mainstream schooling
- b) Remedial school
- c) Training centre
- d) Special care
- e) Home / not placed

7. Renal manifestations

- a) Hematuria
- b) Flank pain
- c) Renal Failure

6. Cardiac manifestations

- a) Arrhythmia
- b) Cardiac failure

8. Ophthalmology review findings



## **APPENDIX 2**

### **INFORMATION LEAFLET ON TUBEROUS SCLEROSIS COMPLEX (TSC)**

(Modified from: Tuberous sclerosis alliance web site, [www.tsalliance.org](http://www.tsalliance.org) information for parents.)

#### **WHAT IS TSC?**

The human body is composed of thousands of tiny units called cells. Genes are the parts of these cells that direct how the cells themselves work. Genes are also the functional units that allow parental features to be passed on to a child. When abnormalities occur in a gene they are called mutations. Tuberous sclerosis complex (TSC) is a condition that results from abnormalities in the genes that are passed on from a parent to a forming fetus.

Tuberous sclerosis complex can be transmitted from a parent to a child (genetic inheritance as explained above) or can occur as a new abnormality in the genes of a child, also known as a spontaneous genetic mutation.

Children have a 50 percent chance of inheriting TSC if one of their parents has this condition. This means that the possibility that a child shall have the condition passed on to them by a parent is the same as that of not inheriting that abnormal gene. They may or they may not get the condition.

At this time, only one of every three TSC cases is known to be inherited. The others are believed to be a result of new abnormalities in the genes a child has (spontaneous mutation). The cause of these mutations is still not well understood.

You will see the condition referred to both as tuberous sclerosis (TS) and tuberous sclerosis complex (TSC).

### **What genes are responsible for TSC?**

Two genes have been identified that can cause tuberous sclerosis complex. Only one of the genes needs to be affected for TSC to be present. The TSC1 gene is located on chromosome 9 and is called the hamartin gene. The other gene, TSC2, is located on chromosome 16 and is called the tuberin gene.

If one were to consider a gene to be a word in a sentence, then a chromosome can be likened to the sentence that gives a cell instructions on what to do and how to do it. If a word is spelt wrongly (mutation) then the instruction would be incorrect.

### **How does a person develop TSC?**

Both the TSC1 and TSC2 genes are believed to control the growth of cells in the body. When either of these genes is defective, cell growth is not regulated and tumors (abnormal growths) occur. The growths are very slow growing and occur in many different organs, primarily in the brain, eyes, heart, kidney, skin and lungs. The genes also play a role in the early fetal development of the brain and skin.

The disease affects some people severely, while others are so mildly affected that it often goes undiagnosed. Some people with TSC experience fits, developmental delay, mental retardation and behavioral problems caused by growths in the brain.

However, there are also many people with TSC living independent, healthy lives and enjoy challenging professions such as doctors, lawyers, educators and researchers.

### **How many people have TSC?**

Current estimates place tuberous sclerosis complex-affected births at one in 6,000. Nearly 1 million people worldwide are known to have TSC. Although we currently do not have an estimate of the total number of people affected in

South Africa, the condition is known to affect all populations with a similar frequency.

**If a parent has a mild form of TSC, will their child with TSC also be mildly affected?**

People with mild cases of tuberous sclerosis complex can produce a child who is more severely affected. In fact, some people are so mildly affected that they may only find out they also have TSC after their more severely affected child receives a diagnosis of TSC.

**How is TSC diagnosed?**

Diagnosis of tuberous sclerosis complex is currently made following a doctor's examination and various tests. These tests include a wood's Lamp examination of the skin to detect changes known to occur in TSC. MRI and CT Scans of the brain are methods used to take detailed images of the brain to detect abnormal growths also known as cortical tubers and astrocytomas. Similarly renal ultrasound and echocardiogram are images that are created using special sound waves that detect abnormal growths in the heart and kidney as well as kidney cysts.

**Do the tumors cause cancer?**

The tumors resulting from tuberous sclerosis complex are non-cancerous, but may still cause serious problems. Tumors that grow in the brain can block the flow of cerebral spinal fluid in the spaces (ventricles) in the brain. This can lead to behavior changes, nausea, headaches or other symptoms.

In the heart, the tumors are usually at their largest at birth, and then decrease in size as the individual gets older. These heart tumors, called cardiac rhabdomyomas, can cause problems at birth if they are blocking the flow of blood or causing abnormal heart beats.

The tumors in the kidney (renal angiomyolipoma) can become so large they eventually affect normal kidney function. Today, doctors are aggressive and

remove individual tumors before they get too large and reduce the function of healthy kidney tissue.

Very rarely (less than 2 percent of) individuals with TSC develop malignant (cancerous) kidney tumors.

### **What is the normal life expectancy of an individual with TSC?**

Most people with TSC will live a normal life span. There can be complications in some organs such as the kidneys and brain that can lead to severe difficulties and even death if left untreated. To reduce these dangers, people with TSC should be monitored throughout their life by their physician for potential problems. Thanks to research findings and improved medical therapies, people with tuberous sclerosis complex can expect improved health care.

### **Since there is no cure, what can be done?**

Follow up with early management of complications helps reduce the impact of TSC on patients. Advances in research are bringing new and improved treatment options. Surgery to remove tumors or stop tumor growth is helping to preserve the function of affected organs. Technology is pinpointing the exact parts of the brain causing seizures which in some cases can be surgically removed. New drugs help control seizures.

### **What are the chances that I shall have another child with TSC?**

If you as a parent have TSC, for each child conceived by you there is a 50% chance that that child shall have TSC as well. That is it is just as likely that they shall have TSC as it is that they shall not have it. If you do not have TSC then the chances that another of your children could have TSC are much lower but there remains a 2% chance that the second child could have TSC.

## **APPENDIX 3**

### **TUBEROUS SCLEROSIS COMPLEX STUDY INFORMATION LEAFLET AND CONSENT FORM**

Principal investigator: Dr Pauline Samia

School of Adolescent and Child Health

Red Cross Children's Hospital

Rondebosch, Cape Town

Contact number: (073) 638 6000

You are invited to take part in a research study involving parents / carers of children who have Tuberous sclerosis complex. We would like to ask for your consent. Please take some time to read the information presented here which will explain the details of the study. Please ask the study staff or doctor any questions about any part of this study that you do not fully understand. It is very important that you are fully satisfied that you understand what the research entails and how you may be involved.

Your participation is entirely voluntary. If you are at all uncomfortable with the process you may contact me (Dr P Samia) or Dr B Schlegel. You are also free to withdraw at any stage, even if you do agree to take part.

This study has been approved by the Committee for Human Research at the University of Cape Town and will be conducted according to the ethical guidelines and principles of the International Declaration of Helsinki, South African Guidelines for Good Clinical Practice and Medical Research Council (MRC) Ethical Guidelines for Research.

#### **What is this research study all about?**

Research done in other parts of the world indicates that a parent's knowledge regarding their child's illness influences how they and how well they understand the course of the illness and required interventions. Less knowledgeable parents are less likely to be compliant with medications, investigations and doctor's appointments. On the other hand adequate knowledge empowers parents when making decisions on behalf of their

children. In this study we seek to establish the level of knowledge parents of children with Tuberous sclerosis have. We shall in addition establish whether provision of written information regarding TSC improves parents' understanding of the condition. We shall do this by asking them a few questions regarding their child's condition as they wait to see the doctor. We shall provide half of the parents with an information pamphlet to go read at home. At the following visit to see the doctor, we shall ask the same questions and compare the results with those obtained at the previous visit.

Children with TSC present in very many different ways. For example some children have profound mental disability while others have normal intellect. By doing this study we would like to help parents of children with TSC understand this condition well and how it affects their individual children. We would like to determine if provision of written information would be an effective way to do this.

**What would participation in this study involve?**

A brief meeting with the study doctor during which you shall be asked a few questions that only require verbal answers.

**Will you benefit from taking part in this research?**

Yes because you shall have an additional opportunity to understand your child's condition. You shall also contribute to the improvement of the TSC service at Red Cross children's hospital.

**Who will have access to your child's records?**

All information collected will be treated as confidential and protected. If it is used in a publication or thesis, the identity of the participant will remain anonymous. The only people who will have access to the information collected will be Dr's Pauline Samia, Dr. Birgit Schlegel and Prof Jo Wilmshurst. As part of the study the research records may need to be reviewed by auditors or the Research Ethics Committee.

**Will you be paid to take part in the study and are there any costs involved?**

No, you will not be paid to take part in the study as information required from you shall only be sought when you come to the doctor for your child's regular check up.

**Is there anything else you should know or do?**

Please don't hesitate to contact Dr Pauline Samia at telephone (073) 638 6000 should you have any further queries or encounter any problems  
You can contact the Committee for Human Research at 021-4066338 (Health sciences faculty, Research Ethics Committee, Room E52-24 Groote Schuur Hospital, Old Main Building, Observatory, 7925) if you have any concerns or complaints that have not been adequately addressed by your study doctor.

**CONSENT**

By signing below, I.....consent to take part in the research study entitled: Parental knowledge and perceptions of Tuberous Sclerosis Complex in children.

I declare that:

I have read or had read to me information regarding the study and the consent form and I fully understand their contents with which I am comfortable.

I have had a chance to ask questions and all my questions have been adequately answered

I understand that taking part in this study is voluntary and I have not been pressurised to take part.

I may choose to leave the study at any time and will not be penalized or prejudiced in any way.

Signed \_\_\_\_\_ at (place) \_\_\_\_\_



3. How is a diagnosis of this condition made?
- a) I don't know 0
  - b) By physical examination 2
  - c) By full clinical evaluation and investigations. 4
4. What body parts or systems do you know are affected by the illness your child has?
- a) Brain 4
  - b) Skin 4
  - c) Kidney 4
  - d) Heart 4
  - e) Eyes 4
  - f) I don't know 0
  - g) Other 0
5. What Investigations do you know can be done to diagnose or monitor TSC in children?
- a) I don't know any 0
  - b) MRI /CT Scan of the brain 4  
(A detailed "picture" of the brain structure)
  - c) Ultrasound of the kidney 4  
(An image of the structure of the kidney created by special sound waves)
  - d) Echocardiogram of the heart 4  
(An image of the structure of the heart created by special sound waves)
  - e) EEG (Electroencephalogram: A record of brain wave activity.) 4
  - f) Woods lamp examination of the skin 4  
(A special light used to examine the skin, allowing better detection of abnormal areas)
6. Can this illness be cured?
- a) I don't know 0
  - b) Yes 0
  - c) No 4

7. What help can be offered to children having the condition your child has?

- |  |   |
|--|---|
| a) Nothing much.   | 0 |
| b) Visit the doctor  | 1 |
| c) Give medications  | 1 |
| d) Address the problems the child has and have regular follow up to look for new problems. | 4 |

8. What problems maybe observed in children with TSC?

- |  |   |
|--|---|
| a) Seizures / fits   | 4 |
| b) Behavioural problems, please specify below              | 4 |
| –  |   |
| –  |   |
| c) Learning difficulties                                   | 4 |
| d) Inability to participate in school /learning activities | 4 |
| e) Inability to participate in social activities           | 4 |

9. To what extent has your child's illness affected the quality of his/her life?

- a) Major negative impact
- b) Some negative effect
- c) No effect.

10. Which issue(s) worry you the most?

- a) Severity of illness
- b) An uncertain future
- c) Cost of medication/ care
- d) Effect of the child's illness on the family
- e) Effect of the child's illness on me as a caregiver
- f) Other

11. Your child attends a clinic that is dedicated to provision of service to children with TSC. Has this been useful?

12. Have you learnt about TSC from any other source apart from the information given to you at the TSC clinic? NO YES (please specify source)  
(Ask on second visit)

University of Cape Town