Clinical and Radiological Assessment of Children with Tuberous Sclerosis

By

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Abstract

Background: Tuberous sclerosis complex (TSC) is a neurocutaneous syndrome that can present at any age and can affect multiple organ systems.

Aim: To assess different presentations and different radiological findings of TSC in children.

Patients and Methods: This retrospective and prospective cohort study was carried out on 20 children aged from 1 month to 16 years old, diagnosed as TSC according to the most recent diagnostic criteria, recruited from Outpatient Clinic of Pediatric Neuropsychiatry Unit, Al-Azhar University Hospital, Assiut, from 1st October 2023 till 30th May 2024**.** All studied patients were subjected to; complete history taking, general, systemic examination, complete neurological examination and complete ophthalmological examination includes slit lamp and fundus examinations. Complete dermatological examination of lesions were examined. laboratory investigations and Radiological investigations: Computerized tomography (CT) brain, Magnetic resonance imaging (MRI), Stanford Binet Intelligence Scale Fourth Edition (SB4), ADHD test according to Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) criteria, Childhood Autism Rating Scale (CARS), Abdominal ultrasonography and Echocardiography were performed to all patients .

Results: Autistic spectrum disorder was present in 4 (20%) patients. Attention deficit hyperactivity disorder (ADHD) was present in 6 (30%) patients. Seizures were present in 15 (75%) patients. Type of seizures was partial in 10 (66.7%) patients, generalized in 5 (33.3%) patients. Regarding CT brain, subependymal calcification was present in 11 (55%) patients and small focal areas of hypodensity at parietal region was present in 1 (5%) patient. Regarding magnetic resonance imaging (MRI) brain, MRI brain, cortical tubercle was present in 1 (5%) patient. Regarding electroencephalogram, focal lesions were present in 11(73.3%) patients, generalized in 4(26.6%) patients. Abdominal US was normal in 18 (90%) patients while multiple renal cysts were present in 2 (10%) patients. Echo was normal in all patients.

Conclusions: Different presentations and different radiological findings of TSC can help in early diagnosis and prognosis of TSC.

Keywords: Clinical, Radiological, Assessment, Children, Tuberous Sclerosis

Introduction

Tuberous sclerosis complex (TSC) is a neurocutaneous syndrome that can present at any age and can affect multiple organ systems. This disorder is usually identified in infants and children based on characteristic skin lesions, seizures, and cellular overgrowth or hamartomas in the heart, brain, kidneys, liver and lungs [1]. This autonomic dominant disorder results from mutations in one of two genes, TSC1 and TSC2, coding for hamartin and tuberin, respectively [2].

The most common neurological manifestations of TSC are epilepsy, cognitive disability, behavioral abnormalities [3]. Diagnosis of TSC is both clinical and genetic. The classic signs and symptoms are mental retardation, seizures and cutaneous lesions, mostly facial angiofibroma [4].

Clinical diagnostic criteria divided into major: hypopigmented macules (≥ 3, with at least 5mm diameter), angiofibroma (≥ 3) or fibrous cephalic plaque, ungual fibromas (≥ 2), shagreen patch, multiple retinal hamartomas, cortical dysplasia, subependymal nodules, subependymal giant cell astrocytoma, cardiac rhabdomyoma, lymphangioliomyomatosis, angiomyolipoma (≥ 2); and minor: "confetti" lesion, enamel pits (> 3), intraoral fibroma (≥ 2), retinal hypopigmented macule, multiple renal cysts and nonrenal hamartomas [5].

Imaging technologies such as ultrasound (US), magnetic resonance imaging (MRI), computed tomography (CT) and echocardiogram (Echo) are always needed for the diagnosis and following up [6].

Cardiac rhabdomyoma, renal angiomyolipoma, and neurologic involvement encompassing cortical or subependymal tubers and white matter (WM) abnormalities are the common radiologic findings [7].

Treatment of TSC is mainly symptomatic, consisting in the management of symptoms associated with the presence of hamartomas in multiple organs and preventing serious functional impairment of these affected organs [5].

A proactive approach involving a multidisciplinary team of doctors from several specialties is imperative in the symptomatic, prophylactic and surgical treatment of TSC [8].

Ethical consideration:

1. Our study was approved by the ethical committee of Faculty of Medicine, Al-Azhar University, Assiut, and conducted in accordance with Helsinki standards 2013.
2. An informed consent was obtained from all parents and participating children.
3. The results and data of the study are confidential, and the patient has the right to keep it.

4.The authors received no financial support for the research, authorship, and/or publication of this article.

5. No conflict of interest regarding study or publications

Sample size calculations:

The sample size calculation was performed using EpI-Info 2002 software statistical package designed by World Health Organization (WHO) and by Centers for Disease Control and Prevention (CDC).
The sample size was calculated based on the following considerations: 95% confidence level and the prevalence of periventricular subependymal nodule was 75 % according to a previous study **(Güngör and Güngör, 2019)** ± 20% confidence limit. one case was added to overcome dropout. Therefore, we recruited 20 cases.

Inclusion criteria:

- Patient diagnosed as tuberous sclerosis complex (TSC) according to the most recent diagnostic criteria.
- Age range 1 month to 16 years.
- Both sexes.

Exclusion criteria:

- Patient with neurocutaneous syndromes other than tuberous sclerosis**.**

Study methods:

This retrospective and prospective cohort study included 20 children aged from 1 month to 16 years old with TSC selected from children attending pediatrics and neonatology outpatient clinics of Al-Azhar University Hospitals, Assiut, Egypt, from 1st October 2023 till 30th May 2024.

All children included in the study were subjected to the following:

I- Full and careful history taking was obtained from patients and their parents Including: name, age, sex, address, order of birth, family history of TSC, age at TSC diagnosis and questions related to the disease manifestations and complications, presence and type of epilepsy, age at seizure onset, type of treatment and response to treatment. History of comorbid conditions including intellectual disability, hyperactivity, inattention and manifestations of autistic spectrum disorders.

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II - Clinical examination which includes: general examination, systemic examination, complete neurological examination and complete ophthalmological examination includes slit lamp and fundus examinations. Complete dermatological examination of lesions were done for all patients with photo taking for all skin lesions.

111- Stanford Binet Intelligence Scale Fourth Edition (SB4), ADHD test according to Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) criteria Childhood Autism Rating Scale (CARS),

1V-Imaging studies including:

abdominal ultrasonography ,Echocardiography. Brain Computerized tomography (CT) and Magnetic resonance imaging (MRI), were performed to all patients .

V-Fundus Ex.

To dect any abnormalities/.

Statistical analysis:

The collected data were analyzed using SPSS v26 (IBM Inc., Chicago, IL, USA). Shapiro Wilks test and histograms were used to evaluate the normality of the distribution of data. Quantitative parametric data were presented as mean and standard deviation (SD). Quantitative non-parametric data were presented as median and interquartile range (IQR). Qualitative variables were presented as frequency and percentage (%).

Results:

All results will be presented in the following tables and photos

There were 16 (80%) male and 4 (20%) female. Age ranged from 0.1 to 18 years with a mean value (± SD) of 8.3 (±6.13) years. There were 8 (40%) patients from urban and 12 (60%) patients from rural. Paternal consanguinity was present in 10 (50%) patients. Family history of similar condition was present in 12 (60%) patients.

Table 1: Demographic data of studied patients

General parameters		N=20
Age (years)		8.3±6.13
Sex	Male	16 (80 %)
	Female	4 (20 %)
	Urban	8 (40 %)
	Rural	12 (60 %)
Positive paternal consanguinity		10 (50 n%)
Family history of similar condition		12 (60 %)

Table (1) Shows the demographic data of the studied cases.

Table 2: Neurological manifestations of studied patients.

Neurological manifestations		N=20
Intellectual disability	Mild	5 (25.0%)
	Moderate	5 (25.0%)
	Severe	1 (5.0%)
Delayed speech		9 (45.0%)
Autistic spectrum disorder		4 (20.0%)
Attention deficit hyperactivity disorder (ADHD)		6 (30.0%)
Seizures (+/-)	Yes	15 (75.0%)
	No	5 (25.0%)
		N=15
Age of onset (years)		1.7±2.48
Type of seizures	partial	10(66%)
	Generalized	5(33%)
Anti seizure medications (ASMS)	Levetiracetam	6(30.0%)
	carbamazepine, Levetiracetam	2(10.0%)
	Sodium valproate	2(10.0%)
	Sodium valprote, Levetiracetam , clonazepam, ACTH	1(5.0%)
	Sodium valproate, Levetiracetam, vigabatrin	1(5.0%)
	Oxcarbazepine	1(5.0%)
	Sodium valprote, Levetiracetam, ACTH	1(5.0%)
	Sodium valprote, vigabatrin	1(5.0%)
Response to treatment		10(66%)

ADHD: Attention deficit hyperactivity disorder, ASMs: anti-seizure medications drugs, ACTH: Adrenocorticotropic hormone, ASD: Autistic spectrum disorder. Mild intellectual disability (IQ:50-69) Moderate intellectual disability (IQ:35-49), Sever intellectual disability (IQ less than 35) according to SB4.

This table Showes that Seizures was the most common neurological manifestation (75%) of TSC patients.

Table 3: Cutaneous and other manifestations of studied patients

		N=20
Cutaneous manifestations	Hypomelnotic macules	20(100.0%)
	Angiofibroma	13(65.0%)
	Ungual fibroma	4(20.0%)
	Shagreen patch	7(35.0%)
	Confetti lesions	2(10.0%)
Other manifestations		
Cardiac rhabdomyoma		0(0.0%)
Ocular features	Multiple retinal hamartomas	1(5.0%)
	Retinal achromic patch	1(5.0%)
Renal features	Multiple renal cysts	2(10.0%)
	Renal angiomyolipoma	0(0.0%)
	Microcalcifications	1(5.0%)
Oral features	Intraoral fibroma	5(25.0%)
	Dental enamel pits	2(10.0%)

Table (3) Showed that Hypomelanotic macules was the most common cutaneous manifestations (100%) of TSC patients.

Table 4: Neuro imaging of studied patients

		N=20
CT brain	Subependymal calcifications	11(55%)
	Cortical calcification	2(10.0%)
	Multiple subependymal calcified nodules	5(25.0%)
	Mild dilated bodies of lat ventricles	1(5.0%)
	Small focal areas of hypodensity at parietal region	1(5.0%)
Echo	Normal	20(100.0%)
		N=3
MRI brain	Normal	1(5.0%)
	Cortical tubers	1(5.0%)
	Subependymal astrocytoma	1(5.0%)
		N=15
EEG	Focal	11(73.3%)
	Generalized	4(26.6%)
Abdominal US	Normal	18(90.0%)
	Multiple renal cysts	2(10.0%)

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Table (4): Regarding neuroimaging study this table showed that subependymal calcifications was found in 11 cases & EEG showed evidence of focal lesions.

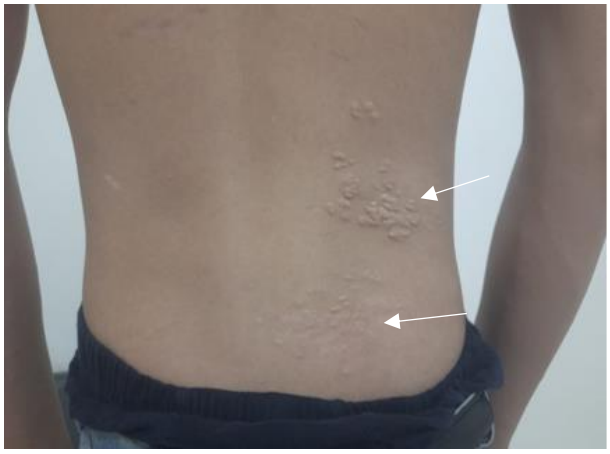

Figure (1): Case No 7**,** male patient 14-year-old with shagreen patch on the right side of the back. He presented by partial epilepsy controlled on carbamazepine and levetiracetam

Figure (2): Case No 9, female patient 12 years-old with Angiofibroma (Sebaceous adenoma) of the face and the scalp. She presented by intractable epilepsy, delayed speech, autism and sever mental delay

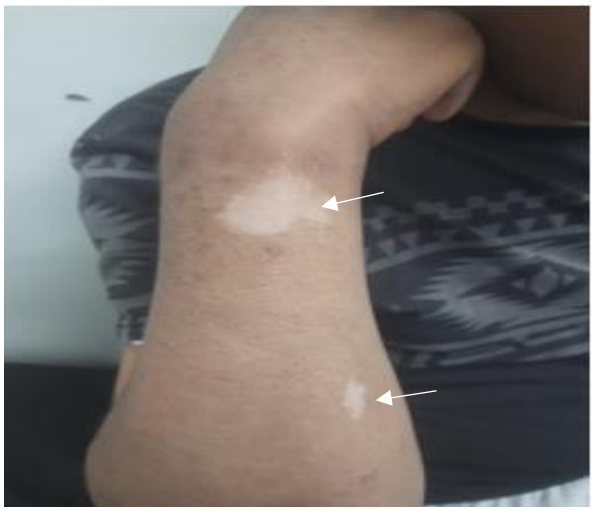

Figure (3): Case No 17, male patient 15 years old with hypopigmented macules (Ash leaf) in the forearm. He presented by moderate mental delay, autism and ADHA

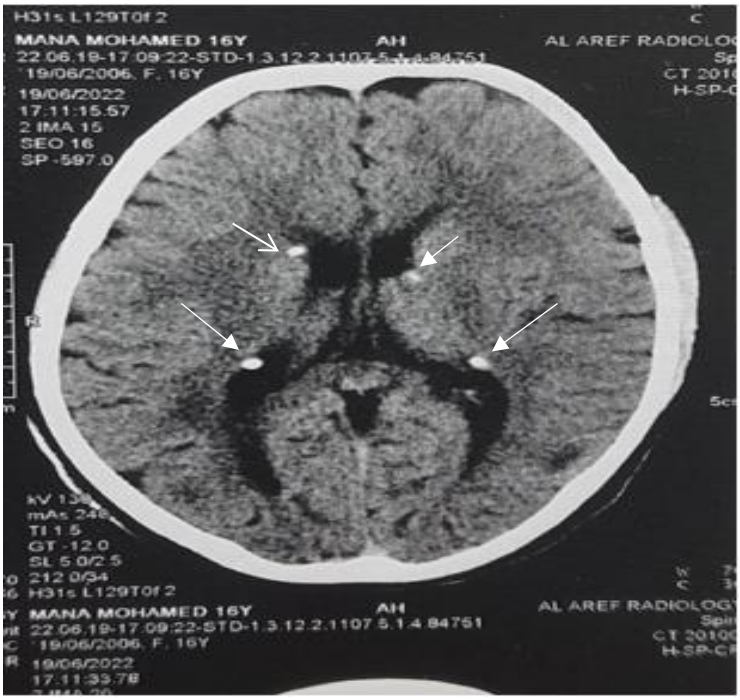

Figure (4): Case No 14, female patient 16-year-old with tuberous sclerosis at the age of 2 years presented by focal convulsion controlled on carbamazepine and levetiracetam. the computerized topography brain showed subependymal calcifications.

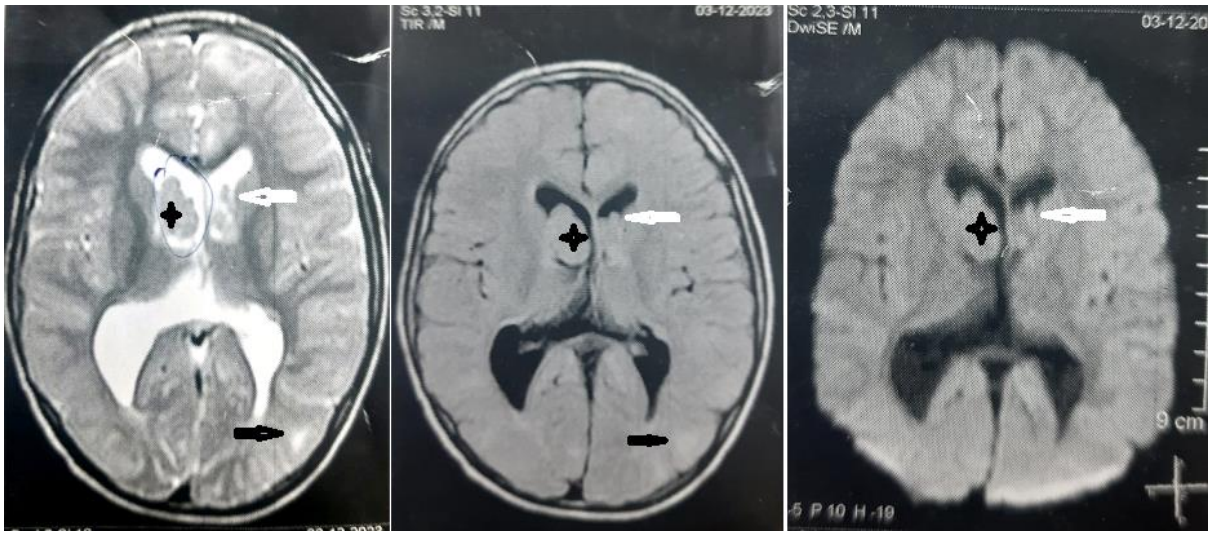

Figure (5): Axial T2, Axial FLAIR and Diffusion of the brain at the ventricular level shows multiple small isointense sub ependymal nodules the largest at the left frontal horn wall (white arrow) associated with multiple sub cortical tubers (black arrow) and large intra ventricular soft tissue mass of giant cell astrocytoma (black star). All lesions show free diffusion.

Discussion

TSC is a neurocutaneous syndrome that can present at any age and can affect multiple organ systems [9].

The study included 20 children diagnosed as tuberous sclerosis recruited from Outpatient Clinic of Pediatric Neuropsychiatry Unit Al-Azhar University Hospital –Assiut (from first October 2023 till 30 May 2024) [10].

There were 16 (80%) male and 4 (20%) female. Age ranged from 0.1 to 18 years with a mean value (± SD) of 8.3 (±6.13) years.

Regarding neurological manifestations of the studied 20 patients, we found that Intellectual disability was mild in 5(25%) patients, moderate in 5 (25%) patients and severe in 1 (5%) patient. Delayed speech was present in 9 (45%) patients. ASD was present in 4 (20%) patients. ADHD was present in 6 (30%) patients.

Nearly similar finding was conducted by **Dulamea et al**. [11] who stated that Intellectual impairment was found in nine patients (40.91%) and **Mammadova et al.** [12] we observed impaired cognitive development in 66.6% of our patients, of whom 50.0% showed severe cognitive impairment. Compared with previous studies reporting a prevalence of cognitive impairment in TSC patients between 50.8 and 60.0% [13]. **Ruiz-Falko et al.** [12] concluded from the recently published TOSCA PASS data that monitoring and reporting of TAND (Tuberous sclerosis associated neuropsychiatric disorders) in patients with TSC in the EU is widely inadequate.

Epilepsy affects 80–90% of individuals with TSC and mostly presents during early infancy; a pharmaco refractory course becomes apparent in more than two-thirds of patients [13]. Tuber/nodule burden, early electroencephalogram characteristics in newborns and infants, infantile spasms, and TSC2 mutation have been proposed as putative early biomarkers of a pharmaco refractory course [13].

In this study we found that seizures were present in 15 (75%) patients. Type of seizures was partial in 10(66%) patients, generalized in 5 (33%) patients

This agreed with a study done by **Mammadova et al.** [12] who revealed that, epilepsy was diagnosed in 85.7% at a mean age of 1.5 ± 2.3 years, and 63.3% of seizures occurred within the first year and 80.0% within the first two years of life. In agreement with our results **Rahman et al.** [14] found that ,the most prevalent form of seizure was focal seizure.

Regarding generalized seizure a similar study done by **Chu-Shore et al.** [15] revealed that about 37% of patients had generalized seizure although most of them had focal onset like our study.

Regarding AEDs, 6 (30%) patients were given Levetiracetam, 2 (10%) patients were given carbamazepine, Levetiracetam, 2 (10%) patients were given Sodium valproate , 1 (5%) patient was given Sodium valprote, Levetiracetam, clonazepam ACTH , 1 (5%) patient was given Sodium valporate, Levetiracetam, vigabatrin ACTH, 1 (5%) patient was given Oxcarbazepine, 1 (5%) patient was given Sodium valporate, Levetiracetam, ACTH and 1 (5%) patient was given Sodium valporate, vigabatrin

This agreed with a study done by, **Welin et al.** [16] revealed that, the most commonly prescribed AEDs were sodium valproate, carbamazepine, levetiracetam, and topiramate.

Regarding cutaneous manifestation of our studied patients. Dermatological manifestations of TSC usually occur in more than 90% of patients, and the specific lesions make up almost half of the major and minor diagnostic clinical criteria, some distinguishable from early infancy.

In agreement with our results, **Mahjoubifard et al.** [13] found that, hypomelnotic macules was in 20 (100%) patients, angiofibroma was in 13 (65%) patients, ungual fibroma was in 4 (20%) patients, shagreen patch was in 7 (35%) patients, confetti lesions was in 2 (10%) patients.

Facial angiofibromas, sometimes erroneously referred to as adenoma sebaceum, are the most visually apparent TSC-associated, often starting to appear within the first 2–5 years of life and ultimately occurring in approximately 75% of patients.

Hypomelanotic macules are often the earliest and most frequently reported cutaneous finding in TSC. They present as hypopigmented macules and patches of various morphologies and should not be confused with de-pigmented patches seen in other pigmentary disorders such as vitiligo. Confetti-like skin lesions, another type of hypomelanotic macule.

In agreement with our results, **Mahjoubifard et al.** [13]. reported to occur in 2.8–28% of patients with TSC. These appear as numerous, small (approximately 1–3 mm in diameter) hypopigmented macules that occur symmetrically; they are typically spread over the distal extremities.

In this study we found that cardiac rhabdomyoma didn't occur in any patient. ocular features, multiple retinal hamartomas were present in 1 (5%) patient and retinal achromic patch was present in 1 (5%) patient. Oral features, intraoral fibroma was present in 5 (25%) patients and dental enamel pits was present in 2 (10%) patients. In a study in which the ophthalmological findings of 100 patients with tuberous sclerosis complex aged between 2 and 76 years were examined, retinal hamartoma was found in 44 of the patients. Retinal achromic patches were found in 39 of the patients. The renal lesions are observed frequently in tuberous sclerosis complex and the frequency increases with age.

In agreement with our results, **Erol et al.** [17] revealed that cardiac rhabdomyoma was not found in any of our patients.

Regarding CT brain, subependymal calcification was present in 11 (55%) patients, cortical calcification was present in 2 (10%) patient, multiple subependymal calcified nodules was present in 5 (25%) patients, mild dilated bodies of lateral ventricles was present in 1 (5%) patient and small focal areas of hypodensity at parietal region was present in 1 (5%) patient

In agreement with our results, **Xu et al.** [18] revealed a scattered distribution of multiple hyperintense nodules in all cases, involving the ependyma of the lateral ventricle, basal ganglia, subventricular area, and body and triangular part of the lateral ventricle.

Regarding MRI brain, MRI brain was normal in 1 (5%) patient, while cortical tubercle was present in 1 (5%) patient and subependymal giant cell tumor was present in 1 (5%) patient.

In agreement with our results, **Fohlen et al.** [19] stated that the mean age at exploration for EEG was 19. Focal seizures were recorded in all patients and IS in five.

Abdominal US was normal in 18 (90%) patients while multiple renal cysts were present in 2 (10%) patients. Echo was

normal in all patients. This is not line with **Mashiwar et al.** [20] found renal lesions, 83.3% of patients had bilateral renal AML and 33.3% (4/12) had renal cysts. In terms of hepatic masses, 5 liver AMLs were detected by abdominal US. In the present study, we reviewed the US imaging features of TSC patients, linking them with pathological mechanisms and clinical profiles, and compared these with other modalities.

Conclusions:

Different presentations and different radiological findings of TSC can help in early diagnosis and prognosis of TSC.

Recommendation:

- Further studies with larger number of sample size and divided to infant or young and older patients to asses difference between them.
- Further studies with longer duration of follow up to assess clinical and radiological changes.
- Further studies focus on genetic assessment and its relation to clinical and radiological findings.
- Further studies on different lines of treatments available for tuberous sclerosis patient and assessment of its effect on their quality of life.
- Further studies to assess the most fatal clinical signs and its relation to mortality rate.

Limitations:

- The study lacks the long duration of follow up to assess clinical, radiological changes and complications related to TSC patients.
- Difficulties in doing some investigation e.g, MRI., genetic studies.
- Expenses of some investigations e.g. genetic (whole exome sequencing).

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