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TUBEROUS SCLEROSIS COMPLEX: CLINICAL SPECTRUM AND EPILEPSY: A RETROSPECTIVE CHART REVIEW STUDY

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Abstract

Tuberous sclerosis complex (TSC) is an autosomal dominant genetic neurocutaneous disorder, with heterogeneous manifestations. We aimed to review the clinical presentation of TSC and its association with epilepsy among Saudi population. This was a retrospective chart review study of 88 patients diagnosed with TSC with or without epilepsy. In 38.6% of patients, symptoms began before 1 year of age. The most frequent initial manifestations of TSC were new onset of seizures (68.2%), skin manifestations (46.6%) and development delay (23.9%). During the evolution of the disease 65.9% had epilepsy, 17% facial angiofibromas, 13.6% Shagreen patch, 18.2% heart rhabdomyomas and 12.5% retinal hamartomas. The genetic study for TSC diagnosis was done for 44 patients, 42 (95,4%) of them were genetically confirmed, for whom 13 patients had TSC1 mutation (29.5%), 29 patients were carrying TSC2 gene mutation (65.9%), Genetic test for TSC 1 and TSC 2 were negative for 2 patients (4.5%) despite positive gene mutation in their relative with TSC. The most common manifestations were central nervous system (predominantly epilepsy) and dermatological manifestations. Most of the patients develop epilepsy with multiple seizure types. TSC 2 mutation is more common than TSC 1 mutation.

Keywords

Tuberous Sclerosis Complex • manifestations • epilepsy • TSC1 • TSC2

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INTRODUCTION

Tuberous sclerosis complex (TSC) is an autosomal dominant genetic multisystem disorder which mainly results from the lack of functional Tsc1-Tsc2 complex due to mutations in TSC1 or TSC2 genes encoding hamartin and tuberin respectively, and belongs to a group of neurocutaneous syndromes together with Sturge- Weber syndrome, von Hippel-Lindau disease, and neurofibromatosis [1,2]. Pathologically, TSC is defined as a disorder of cell migration, proliferation and differentiation. [3] The incidence rates of TSC were estimated to be 1 /6,000 and 1 /10,000 [1,4,5] among live births; however previous studies [2,6] reported that there are undetected mild TSC cases and this makes the true incidence likely to be higher. Mutations in TSC1or TSC2 genes were found in approximately 85% of patients with TSC [7,8]. The role of TSC1-TSC2 protein complex is an upstream regulator of mammalian target of rapamycin (mTOR), any disruption of this function results in over activation of mTOR and dysregulated growth control, hence explaining the fundamental pathological mechanism of TSC disorder [1,9].

The clinical diagnosis of TSC is challenging as the disease is highly variable in clinical presentation, findings, and its manifestations continue to develop over the lifetime of the affected individuals and can vary widely between even closely related individuals [10]. In the recommendations of the 2012 international TSC consensus conference for TSC diagnostic criteria update [10], the new inclusion of genetic testing results was one of the key changes compared with 1998 criteria, keeping on the point that Clinical features of TSC continue to be a principal means of diagnosis with the presence of two major features or one major plus two minor features for a definitive diagnosis.

TSC is characterized by the development of hamartias (non-growing lesions) and hamartomas which represent the primary manifestations of the disease and affect various organ systems involving the central nervous system (CNS), dermatological (facial angiofibromas), kidneys (renal angiomyolipoma), Circulatory (cardiac rhabdomyoma), eyes (retinal hamartomas) and respiratory [1,10,11]. Usually, the first detected manifestations are infantile spasms, neurodevelopmental and skin manifestations also typically present early in life, on the other hand, renal manifestations are often observed in adolescence or adulthood and respiratory manifestations are typically present in adult and almost exclusively symptomatic in female TSC patients [2,10].

The CNS is the most commonly and severely affected systems in TSC patients, where brain MRI imaging frequently shows structural abnormalities including cortical tubers and subependymal nodules (SENs), which can transform into subependymal giant cell astrocytomas (SEGA), and consequently, patients with TSC often suffer from debilitating neurological defects including epilepsy, mental retardation, and autism spectrum disorder (ASD) [12]. In recent times, these

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structural abnormalities and pathological changes were thought to be responsible for TSC patients neurological phenotype; however, current studies have proposed that subtler microscopic changes like aberrant white matter connectivity, which cannot be envisioned with regular MR imaging techniques, play a role in causing epilepsy, ASD, behavioral problems and cognitive deficits [13]. Previous studies reported that epilepsy is the most common and troublesome symptom in TSC patients, seen in 80–90% of the affected individuals, often refractory to treatment and a significant source of morbidity and mortality [14].

Epilepsy begins in the first year of life in majority of the patients with TSC and is very difficult to handle, and poor control together with early onset of seizures are considered as traditional risk factors for poor neuropsychological outcome among those patients [2,15,16]. Epilepsy usually begins in the first three years of life although onset at any age is a possibility. Drug resistant epilepsy is found most commonly in TSC patients. Seizures are classified by ILAE into 3 major categories; focal onset, generalized onset and seizure of unknown onset. Generalized seizures occupy a large portion of brain, it originates at some point and rapidly engages bilaterally distributed networks but not necessarily the entire cortex. Focal seizures on the other hand limits to one hemisphere. Generalized seizure might be of motor onset like tonic- clonic or other motor onset, or it can be of nonmotor onset like absence. Focal are optionally classified as aware or impaired awareness. Impaired awareness and loss of consciousness are not the same. If the awareness is impaired at any time during a seizure, impaired awareness should be included. After the level of awareness, focal is classified as of motor onset or nonmotor onset. The expanded classification includes subdivision focal to bilateral tonic clonic. For generalized seizures level of awareness is omitted as awareness is mostly impaired in most generalized seizures. Unknown onset refers to seizures in which the onset is unknown but other manifestations are known, it is also classified as having motor (tonic clonic or other motor) or nonmotor onset. It is further clarified as unclassified for the events that are clearly seizures yet unclassifiable [17]. The prevalence of ASD and intellectual disability among TSC patients was reported to be 17-50% and 60%, respectively [1,2,18,19]. Additional neuropsychiatric problems including aggressive/disruptive behavior, attention-deficit/hyperactivity disorder (ADHD), anxiety and depression have been reported in some TSC patients [12].

Data about TSC and its clinical manifestations are scarce in Saudi Arabia and even the whole Gulf Cooperation Council (GCC) countries. The lack of such data that gather information across the broad spectrum of manifestations, analyze the combinations of the involved organ systems and document the age of onset, description of seizure and its management and progression of clinical features will compound barriers to improve the quality and coordination of care in TSC. In the current study, we used patients' charts to study the natural history of TSC in a cohort of patients in Saudi Arabia. The aim of this study was to review the clinical presentation of TSC, its association with epilepsy and the natural history of epilepsy in this genetic disease among Saudi population.

METHODS

We included all patients (88) with a confirmed diagnosis of TSC (based on 2012 International Tuberous Sclerosis Complex Consensus Conference) with or without epilepsy in the period between 1999-2016. Predesigned questionnaire included questions that covered the patients' demographic information, clinical and neurological manifestations, seizures description, antiepileptic drugs, systemic examinations (CNS, skin, heart, kidney, and eyes), genetic study, neurophysiology (electroencephalography (EEG)) and imaging (MRI, CT, USG abdomen and others) was used to collect the data.

We performed a retrospective chart review study. Charts of the 88 patients were reviewed for the above mentioned items, and the genetic, clinical and neurological manifestations and outcomes were described based on patients' last visit. Genetic testing of the TSC1 and TSC2 genes was performed.

Statistical analysis

Data were analyzed by using Statistical Package for Social Studies (SPSS version 22). Chi-square test and Fisher's exact test were used for categorical variables. A p-value <0.05 was considered statistically significant.

Ethical Approval

The study was approved by the research ethics committee at King Faisal Specialized Hospital & Research Center (KFSH&RC) (ORA#2151057)

RESULTS:

A total of 88 patients with confirmed TSC diagnosis were included in the current study. The cohort had a mean age of 16.56±14.21, the highest percentage of them (23.9%) were in the age group of 11-14 years old followed by 22.7% aged 7-10 years old. (Table 1).

The highest percentage (38.6%) of the participants had age of onset less than one year for the first time of symptoms presentation, followed by 30.7%, 15.9%, and 14.8% at the age of 1- 5, 6-10, and > 10 years, respectively. (Fig. 1)

Seizure was the highest prevalent symptom of TSC among the studied cohort accounting at 68.2% followed by skin manifestations at 46.6% and development delay at 23.9% (Table 2).

Seizures and skin manifestations were highly prevalent in males compared to females (69.6% and 48.2% versus 65.65% and 43.8%, respectively). On the other hand, the prevalence of global development delay was higher in females compared to males (25% and 23.2%, respectively). The prevalence of other manifestations including delayed learning, ADHD, and autism, were as following: 11.4%, 11.4%, 6.8%, and 9.1% respectively (Table 3).

The patients were categorized according to their age groups into two groups: <14 (children) and ≥14 years old (adults). It was observed that the prevalence of skin manifestations, development delay, ADAH and autism was higher in children compared to adults (48%, 29%,12% and 10% versus 24%, 17%, 0% and 8%, respectively) (Table 4).

When symptoms were compared by the time of its first presentation, the highest prevalence of each of the assessed symptoms was as following: seizures (78.6%) at the age of onset

Table 1: Demographic characteristic

	N	%
Age (mean ± SD)	16.56±14.21	
<6 y	11	12.5
7-10y	20	22.7
11-14y	21	23.9
15-18y	10	11.4
19-25y	13	14.8
>25y	13	14.8
Gender		
Male	56	63.6
Female	32	36.4
Birth place (Region)		
Central	41	46.6
Eastern	10	11.4
Western	8	9.1
Southern	11	12.5
Northern	17	19.3
Other	1	1.1

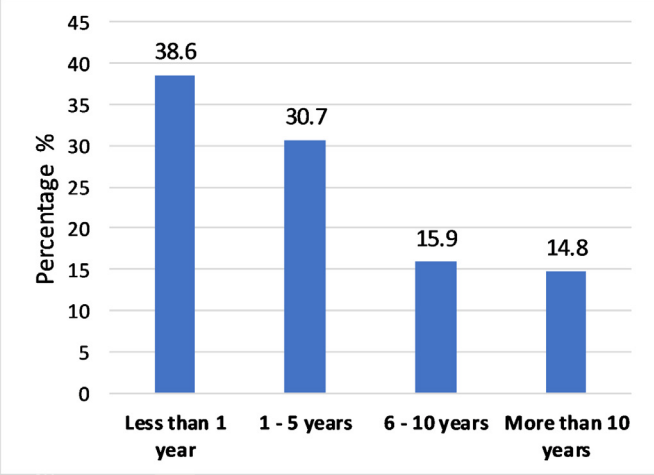

Fig. 1: Time of first presentation of symptoms

Table 2: Clinical manifestations of TSC among the studied cohort

Symptoms	N	%
Seizures	60	68.2
Skin Manifestations	41	46.6
Developmental Delay	21	23.9
Delayed Learner (MR)	10	11.4
Delayed Language	10	11.4
ADHD	6	6.8
Autism	8	9.1
Other	6	6.8

from 6-10 years, skin manifestations (64.7%) at less than one year (P <0.01), development delay (32.4%) at less than one year (P <0.31), delayed learning and delayed language (23.1% for each) at time from >10 years (P <0.48 and <0.20, respectively), and ADAH autism and others (14.3% for each) at age of onset of 6-10 years (Table5).

The genetic study for TSC diagnosis was done for 44 patients, 42 (95.4%) of them were genetically confirmed, for whom 13 patients had TSC1 mutation (29.5%), 7 of them were females (53.8%). 29 patients were carrying TSC2 gene mutation (65.9%), 20 of them were male (68.9%). Two (4.5%) patients had their genetic test for TSC1 and TSC2 negative despite positive gene mutation in their relative with TSC. Three patients who were genetically confirmed with TSC2 also had a mutation in PKD1/PKD2 gene of autosomal dominant polycystic kidney disease which indicates more severe form of the disease (Table 6).

Half of the patients had sphincter control during the seizures. Seizures age of onset was less than one year in 61.0% of the patients. For the number and type of antiepileptic drugs used in our cohort, Carbamazepine (Tegretol) was the most commonly used (42.3%), followed by Levetiracetam (Keppra) (39.4%), Valproic acid (Depakine|) (36.6%), and Vigabatrin (Sabril) (31.0%). The seizure was controlled only in 54.5% of the patients. The seizures observed were 49 generalized seizures, 16 focal seizures, 14 were only spasms and 4 were unable to describe the type of seizure.

Systemic examinations of the studied cohort were reviewed for skin examinations, Cardiac Rhabdomyoma, prevalence of kidney complications, eye examinations, prevalence of seizures and Global Development Delay (GDD) (Table 7).

The results of psychological evaluation showed that, among the studied TSC cohort, the prevalence of ADHD and autism was 26.1% and 17%, respectively, being higher in patients aged <14 at 28.85% and 19.23% compared to those aged ≥14 at 22.22% and 13.89% respectively, but the difference was non-significant in both cases (P <0.23 and <0.25,

respectively).

DISCUSSION

To the best of our knowledge, the current study represents the first study reporting the clinical spectrum and epilepsy among TSC patients in Saudi Arabia and the whole Gulf Cooperation Council (GCC) countries. It might contribute towards a better understanding of the disease complexity and its management in the community setting. We reported comprehensive data on known TSC manifestations, including their prevalence, age of onset and their differences by age, gender and the time of their presentations.

In contrast to what had been previously reported in the literature [7,8], the current study has a higher percentage of patients with genetically confirmed TSC genes (TSC1 and TSC2) mutations (85% versus 95,4%). TSC2 mutation was higher than TSC1, a finding which is in line with Dabora SL *et al* study [20].

The prevalence of seizure as one of the initial TSC manifestations was lower compared to what had been recently reported from a study published in 2017 by Rubilar C. et al [21] at 68.2% and73.85% respectively, while the same study reported a lower prevalence of delayed development (4.8%)compared to the current one (23.9%).

Against what we expected based on previous research studies, a lower prevalence of some manifestations was recorded. These manifestations include seizures, autism and delayed learner, where previous studies reported a prevalence of 80-90%, 17-50% and 60%, compared to 65.9%, 17.0% and 11.4%, respectively in the current study [1,2,14,18,19]. Similarly, the prevalence of cardiac rhabdomyomas, facial angiofibroma, shagreen batches, ungula fibroma, and retinal hamartomas at 18.2%, 17.0%, 13.6%, 1.1%, and 12.5%, respectively, was lower compared to a similar study in which the prevalence of these manifestations was 47.6%, 47.6%, 23.8%, 12.0% and 35.7%, respectively [21]. Such difference is probably likely to represent under-diagnosis and/or under reporting of the manifestations, highlighting inadequate care and improper data recording. Northrup H et al. reported

Table 3: Symptoms of TSC by gender

	Male		Female		P value
Symptoms	N	%	N	%	
Seizures	39	69.6	21	65.6	0.697
Skin Manifestations	27	48.2	14	43.8	0.686
Developmental Delay	13	23.2	8	25.0	0.85
Delayed Learner (MR)	7	12.5	3	9.4	0.657
Delayed Language	6	10.7	4	12.5	0.8
Behavioral Problems-ADHD	4	7.1	2	6.3	0.873
Behavioral Problems-Autism	6	10.7	2	6.3	0.483
Other	1	1.8	5	15.6	0.013

Table 4: Symptoms of TSC by age group

	age ≤ 14		age > 14		P value
	N	%	N	%	
Seizures	34	65	26	72	0.498
Skin Manifestations	25	48	16	44	0.737
Developmental Delay	15	29	6	17	0.188
Delayed Learner (MR)	2	4	8	22	0.008
Delayed Language	5	10	5	14	0.535
Behavioral Problems-ADHD	6	12	0	0	0.035
Behavioral Problems-Autism	5	10	3	8	0.837
Other	3	6	3	8	0.639

Table 5: Symptoms by the time of the first presentation

	Less than one year		From 1 to 5 Years		From 6 to 10 years		More than 10 years		P value
	N	%	N	%	N	%	N	%	
Seizures	26	76.5	18	66.7	11	78.6	5	38.5	0.069
Skin Manifestations	22	64.7	12	44.4	6	42.9	1	7.7	0.006
Developmental Delay	11	32.4	6	22.2	1	7.1	3	23.1	0.315
Delayed Learner (MR)	4	11.8	2	7.4	1	7.1	3	23.1	0.486
Delayed Language	2	5.9	2	7.4	3	21.4	3	23.1	0.202
Behavioral Problems-ADHD	2	5.9	2	7.4	2	14.3	0	0.0	0.524
Behavioral Problems-Autism	2	5.9	3	11.1	2	14.3	1	7.7	0.79
Other	2	5.9	1	3.7	2	14.3	1	7.7	0.636

Table 6: Seizure description

	N	%
Body		
Whole Body	42	47.7
Right Sided	6	6.8
Left Sided	16	18.2
One Leg	1	1.1
One Arm	8	9.1
Cannot Describe	6	6.8
Movement		
Clonic Jerks	2	2.3
Stiffness (Tonic)	14	15.9
Tonic and Clonic (Jerking and Stiffness)	33	37.5
Myoclonic Jerks	16	18.2
Infantile Spasm	14	15.9
Cannot Describe	4	4.5
Atonic	0	0.0
Gelastic Seizures	0	0.0
Eyes		
Upward Gaze	19	21.6
Closed Eyes	0	0.0
Right Deviation	1	1.1
Left Deviation	6	6.8
Stare	9	10.2
Blink and Stare	8	9.1
No Change	4	4.5
Cannot Tell	15	17.0
Twitching	0	0.0
Skin Color		
Blue	11	12.5
Pale	4	4.5
No Change	32	36.4
Cannot Describe	16	18.2
Missing	25	28.4
Sphincter Control	44	50.0
Mouth		
Dry	4	4.5
Drooling	5	5.7
Foam	2	2.3
Tongue Bite	1	1.1
Cannot Describe	1	1.1
How Often?		
Daily	35	39.8
Weekly	9	10.2
Monthly	3	3.4
Other	13	14.8
Condition After Seizure		
Asleep	13	14.8
Drowsy	8	9.1
Alert	12	13.6
Confused	8	9.1

that cardiac rhabdomyomas are the main characteristic of TSC which require cardiological follow-up with echocardiography [10].

On the other hand, the prevalence of Angiomyofibroma reported in the current study was higher compared to that reported by Rubilar C. et al at 26.1% and 16.7%, respectively, while a slightly higher prevalence of renal cyst was reported compared to the same study (14.8% and 14.3%) [21].

In majority of the patients the initial manifestations were detected before the first year of life, which is in line with what is reported in the literature [22]. In most patients the onset of seizure was earlier than 1 year of age which are rarely observed in patients without this disease [10], therefore, the lower prevalence reported in our study emphasize the importance of addition to early onset, epilepsy was difficult to manage, requiring administration of two or three antiepileptic drugs with poor outcomes, a finding similar to the reported in previous studies [2,15,16]. Only 15.9% of the patients with epilepsy evolved with infantile spasms, which is lower than reported in the literature, which describes a frequency of infantile spasms of 48.7% [21]. Vigabatrin is the first line treatment of focal seizures in infant TSC patients. Then other Antiepileptic drugs (AEDs) are given such as ACTH which is effective for infantile spasms in TSC patients. If first line treatment has failed, AED combination therapy should be initiated. If two consecutive AEDs fail, presurgical evaluation is recommended. Surgery marks the highest probability to abolish seizures. In nonsurgical patients or patients who fail surgeries, ketogenic diet is suggested. After ketogenic diet, vagus nerve stimulation is the option [23].

In accordance with the literature [20], our results showed that ungual fibromas are less common compared to some other TSC skin findings, with a higher frequency in older patients, and its later onset, typically in the second decade or later [24], is the cause of the greater frequency in adults. Thus, their usefulness in diagnosis is usually limited to adolescents and adults. The current study result in regards to a significant higher prevalence of facial angiofibroma in adults is in contrast to

what had been previously reported that its onset among TSC patients typically ranges between ages 2 and 5 years [25].

Renal manifestations are considered an important source of morbidity and mortality in TSC. In a published study that assessed mortality associated with TSC [26], renal problems were the second leading cause of premature death after severe intellectual disability. The two renal pathologies most commonly seen in TSC are angiomyolipomas and cysts, the first are more prevalent, and the frequency of renal lesions were positively correlated with age [27]. These findings are in agreement with the current study.

Limitations: The limitations for the current study are typical for retrospective studies, where data are limited by the level of detail and quality of information recorded. The prevalence of some manifestations is likely to be under reported.

CONCLUSION

The study shows the nature of TSC among Saudi population, with patients presenting with a broad spectrum of manifestations, the prevalence of which was estimated and the most common manifestations were central nervous system (predominantly epilepsy) and dermatological manifestations, the estimated prevalence was mostly lower compared to the literature. Most patients develop epilepsy with multiple seizure types and they did not achieve seizure freedom however; most of them were controlled on 2-3 antiepileptic medications.

Table 7: Complications of TSC by age groups

	All		Age<14 y		Age≥14y		P value
Skin	**N**	**%**	**N**	**%**	**N**	**%**	
Hypopigmented Macules (Ash Leaf Spots)	47	53.4	28	53.85	19	52.78	0.921
Shagreen Patch	12	13.6	4	7.69	8	22.22	0.063
Facial Angiofibroma/Adenoma Sebaceum	15	17.0	5	9.62	10	27.78	0.026
Gingival Fibroma	0	0.0	0	0.00	0	0.00	
Periungual Fibroma	1	1.1	0	0.00	1	2.78	0.409
Other	6	6.8	1	1.92	5	13.89	0.040
Cardiac Rhabdomyoma	16	18.2	13	25.00	3	8.33	0.023
Kidney							
Polycystic Kidney	4	4.5	2	3.85	2	5.56	0.491
Renal Cyst	13	14.8	6	11.54	7	19.44	0.804
Angiomyofibroma	23	26.1	9	17.31	14	38.89	0.136
Eye							
Retinal Hamartoma	11	12.5	7	13.46	4	11.11	0.526
CNS(Seizures)	58	65.9	36	69.23	22	61.11	0.002
GDD	34	38.6	24	46.15	10	27.78	0.003
Movement Disorder	7	8.0	3	5.77	4	11.11	0.557
Psychological Evaluation							
ADHD	23	26.1	15	28.85	8	22.22	0.231
Autism	15	17.0	10	19.23	5	13.89	0.252

TSC 2 mutation is more common than TSC 1 mutation. TSC 2 mutation is more common in male. On the other hand, TSC 1mutation is almost equal in both genders with slight female predominance. A very little number of patients (4.5%) can have negative gene test in presence of clinical manifestation of TSC.

DISCLOSURE

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Conflicts of interest: None

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