Review of the spectrum of tuberous sclerosis complex: The Saudi Arabian Experience

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ABSTRACT

الأهداف: تحديد مدى انتشار مرض التصلب الحدبي المعقد (TSC) بين الأطفال السعوديين ووصف الأعراض السريرية، والنتائج الجلدية العصبية، ونتائج التصوير العصبي، ومضاعفات المرض.

المنهجية: تم اختبار ما مجموعه 61 مريضاً من مرضىTSCالمؤكدين وراثياً من الشؤون الصحية بالحرس الوطني (NGHA) في المملكة العربية السعودية. من هذا التحليل الوصفي بأثر رجعي. تم عرض البيانات باستخدام الاحصاءات الوصفية.

النتائج: وجد أن متوسط العمر عند التشخيص هو 4.9 سنة. كانت العقيدات تحت البطانة العصبية (86.9%)، والدرنات القشرية العديدة و/أو خطوط الهجرة الشعاعية (63.9%)، والبقع تحت الميلانينية (63.9%) هي المعايير الثلاثة الأكثر شيوعًا. كانت الغالبية العظمى (86.9%) ممن تم تشخيصهم مصابين بالصرع، وكان 50% منهم يعتبرون مستعصيين على العلاج من الناحية الطبية. ما يقرب من نصف الأشخاص الذين خضعوا للفحص خضعوا للاختبارات الجينية، والتي كشفت أن TSC2 طغى على TSC1. كانت أعراض الاضطرابات النفسية العصبية المرتبطة بالتصلب الحدبي (TAND) موجودة في 66.7% من مرضى TSC1 و73.9% من مرضى TSC2.

الخلاصة: توضح نتائج هذه الدراسة أن الطيف السريري لـ TSC بين الأطفال السعوديين يتوافق مع نتائج الدراسات السابقة. كان TSC2 أكثر انتشارًا من TSC1. وكانت العلامات الأكثر شيوعا هي الجلدية والعصبية. تعد مراقبة مرضى TSC بانتظام أمرًا بالغ الأهمية لتحديد أي مشكلات في أسرع وقت ممكن.

Objectives: To determine the prevalence of tuberous sclerosis complex (TSC) in the paediatric Saudi population and to characterise the range of clinical symptoms, neurocutaneous findings, neuroimaging results, and complications of the disease.

Methods: A total of 61 genetically confirmed TSC patients from the National Guard Health Affairs (NGHA) in Saudi Arabia were the subject of this retrospective descriptive analysis. The data were presented using descriptive measures.

Results: The mean age at diagnosis was found to be 4.9 years. Subependymal nodules (86.9%), numerous cortical tubers and/or radial migration lines (63.9%), and hypomelanotic macules (63.9%) were the 3 most common significant criteria. The vast majority (86.9%) of those diagnosed had epilepsy, of which 50% were considered medically intractable. Nearly half of our subjects underwent genetic testing, which revealed that TSC2 predominated over TSC1. Symptoms of Tuberous Sclerosis Complex-Associated Neuropsychiatric Disorders (TAND) were present in 66.7% of TSC1 patients and 73.9% of TSC2 patients.

Conclusion: The findings of this study demonstrate that the clinical spectrum of TSC among Saudi children is consistent with the body of existing literature. The TSC2 was more prevalent than TSC1. The most frequent signs were cutaneous and neurological. Monitoring TSC patients regularly is crucial to identify any issues as soon as possible.

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Tuberous sclerosis complex (TSC) is a rare neurocutaneous disease; one of its remarkable features is the presence of benign tumour-like lesions known as hamartomas. Regardless of gender or race, it has autosomal dominant inheritance with a frequency of 1 in 20,000 and an estimated incidence of 1 in 6,000 to 10,000 in the general population.[1] Although TSC is inherited as an autosomal dominant characteristic, two-thirds of all TSC appear sporadically with apparent de novo mutations that need the acquisition of a second somatic hit to be diseased.[2,3] Around 10% to 15% of people who formerly met the TSC clinical criteria by traditional genetic testing were categorised as having no mutation identified in either TSC1 or TSC2.[4,5] However, the diagnosis of TSC should not be ruled out only because a causal mutation could not be found. Mosaicism and intronic mutations may be the hidden cause, according to recent research.[6]

Due to their uniqueness to TSC, numerous cortical tuber migration lines have taken the position of cortical dysplasia in the new recommendations. Importantly, a diagnosis may only be made if at least 2 significant traits or one major and 2 minor features are present. Alternately, molecular genetic testing can be used to diagnose the existence of pathogenic mutations in TSC1 or TSC2.[7] The initial signs of TSC are epileptic spasms, neurodevelopmental delay, and cutaneous hypopigmented macules; renal angiomyolipomas appear later, in adolescence or adulthood.[8,10] One of the late indications of lymphangioleiomyomatosis (LAM), pulmonary involvement, shows a female preponderance.[11] Subependymal nodules, cortical dysplasias, and subependymal giant cell astrocytomas are additional central nervous system diseases that affect 5%–15% of people with TSC.[10] Patients with TSC 2 exhibit far more severe symptoms than those with TSC1, and they are more likely to experience epileptic spasms, kidney cancer, intellectual impairment, autism, and low intelligence quotient.[12-14]

One of the most prevalent neurological symptoms of TSC is epilepsy, which is also a known source of morbidity and death in these individuals. In most cases, epilepsy develops in the first few months of life.[15] In a study by Nabbout et al[16], 83% of TSC patients experienced epilepsy, (of whom 67.5% had focal seizures and 38.9% had epileptic spasms). Few TSC patients with epilepsy were able to obtain a remission of their seizures following a trial of stopping antiseizure drugs (ASMs), according to the findings by Sparagana et al.[17] However, patients with minor cerebrum damage are the ones who have this remission.[17] Similar results from local retrospective research showed that the majority of TSC patients had seizures upon presentation. However, intriguingly, the prevalence of epilepsy among TSC patients was lower in Saudi Arabia than in Western nations.[18]

Even though more than 90% of TSC patients are impacted by one or more Tuberous Sclerosis Complex Associated Neuropsychiatric Disorders (TAND) features, the expectation is that only 20% of individuals with TAND will obtain a full examination.[19] One of the behavioural symptoms that have been linked to TSC is autism, although the exact mechanism underpinning this relationship is still unclear.[20] Autism spectrum disorder (ASD) was identified in 40.5% of individuals with TSC in research by Vignoli et al.[21] There are limited studies in Saudi Arabia that examine the prevalence of TSC and its associated characteristics. Previous studies in Saudi Arabia focused on specific neurological symptoms of TSC, such as epilepsy,[18] or examined whether children with TSC received appropriate surveillance as advised by TSC Consensus Recommendations.[22] Therefore, this study aims to determine the prevalence of TSC in the paediatric Saudi population and to characterise the range of clinical symptoms, neurocutaneous findings, neuroimaging results, and complications of the disease.

Methods. *Study design, setting, and sample size.*

This is a retrospective chart review study conducted at the National Guard Health Affairs (NGHA), Saudi Arabia. The NGHA is a renowned healthcare institution in Saudi Arabia that primarily caters to the healthcare needs of military and civilian personnel affiliated with the Saudi Arabian National Guard, along with their dependents. It is a comprehensive and expansive institution that offers an extensive array of medical services, encompassing both general and specialist treatment, as well as engaging in research and educational endeavors.

All patients diagnosed with TSC, based on the Updated International Tuberous Sclerosis Complex Diagnostic Criteria and Surveillance and Management Recommendations 2021, were eligible to be part of this study.[7] Using non-probability consecutive sampling, the charts of 61 TSC patients following up at NGHA in 4 cities (Riyadh, Jeddah, Madinah, Al-Ahsa, and Dammam) from January 2016 to December 2022 were reviewed for data extraction.

The term "drug-resistant epilepsy" (DRE) was used in this study to describe epilepsy patients who received surgery or vagus nerve stimulation (VNS) for seizure control and those in whom 2 or more antiseizure drugs (ASMs) failed to control their seizures.[24,25] The term "Tuberous Sclerosis Complex Associated

Neuropsychiatric Disorders" (TAND) is used to refer to the clinical and functional aspects of TSC that are connected. If TSC patients have behavioural, mental, or intellectual signs, they will be regarded as having TAND in this research.[19]

Patients of both genders (adults and pediatrics) who are diagnosed with TSC using revised diagnostic criteria (Updated International Tuberous Sclerosis Complex Diagnostic Criteria and Surveillance and Management Recommendations - 2021) were included in this study.[7] The diagnosis of TSC is established with one of the following: 1) genetic diagnosis (a pathogenic variant in TSC1 or TSC2 by molecular genetic testing is diagnostic for TSC) or 2) definite TSC (2 major features or 1 major feature with 2 minor features). Major criteria included hypomelanotic macules (≥3; at least 5 mm diameter), angiofibroma (≥3) or fibrous cephalic plaque, ungual fibromas (≥2), Shagreen patch, multiple retinal hamartomas, multiple cortical tubers and/or radial migration lines, subependymal nodules (≥2), subependymal giant cell astrocytoma, cardiac rhabdomyoma, lymphangiomyomatosis, and angiomyolipomas (≥2). Minor criteria included "Confetti" skin lesions, dental enamel pits (≥3), intraoral fibromas (≥2), retinal achromic patch, multiple renal cysts, nonrenal hamartomas, and sclerotic bone lesions. Patients with the combination of lymphangiomyomatosis and angiomyolipomas without other features were excluded as they did not meet the inclusion criteria for a definite diagnosis of TSC.

Study instrument and statistical analysis. The patients' demographic information (gender, age, and length of follow-up), clinical TSC symptoms and radiological findings, TAND, electroencephalography (EEG) results, ASMs, surgical results, and genetic research results were all included in the data collection.

Ethical approval. The Institutional Review Board (IRB) was approved by King Abdullah International Medical Research Center (KAIMRC) (IRB/2611/21). No participant identities or medical record numbers were used. For patient confidentiality purposes, each patient was instead identified by a serial number. Before taking or using any photographs for this study, patients and/or their families gave their consent. The study was designed and conducted in accordance with the ethical principles that have their origins and comply with the Declaration of Helsinki.

Statistical analysis. IBM Corp., Armonk, New York, USA, SPSS version 27.0 was used for the statistical analysis. In this study, continuous variables were described using mean and standard deviation (SD), whereas categorical variables were represented using frequencies and percentages. All categorical variables were cross-tabulated, and the proportional Chi-square test was used to identify any significant differences. Additionally, a cross-tabulation employing an independent t-test was used to determine any significant differences in terms of the gender or age at which TSC characteristics first appeared. Statistical significance was defined as a *p*-value of 0.05.

Results. The present study included a total of 61 patients diagnosed with TSC. A total of 36 (59%) were males, while 25 (41%) were females. The mean age of the patients at the time of diagnosis was estimated to be 4.9 years (**Table 1**). The average duration of follow-up was approximately five years. Only nine (13.1%) of the patients had a first-degree relative with TSC.

In this sample, the presence of subependymal nodules was the most prevalent main criterion at 86.9% (n=53), followed by multiple cortical tubers and/or radial migration lines at 63.9% (n=39) and hypomelanotic macules at 63.9% (n=39). Multiple renal cysts were the most prevalent minor criterion at 27.9% (n=17). Based on the Updated International Tuberous Sclerosis Complex Diagnostic Criteria and Surveillance and Management Recommendations 2021,[9] **Tables 2 and 3** display the frequency of the diagnostic criteria and the age at presentation in the cohort studied

Hypomelanotic macules were significantly more prevalent in males compared to females, accounting for 77.8% and 44%, respectively (*p*=0.007) (**Table 4**).

Multiple cortical tubers and/or radial migration lines appear earlier in males (2.7±3) than in females (6.7±6.6), as shown in **Table 5**. A total of 11 (18%) of the 61 patients included in this study had oral complications such as dental cavities. However, the evidence was not conclusive that any of our patients had pitted dental enamel.

Nearly nine-tenths (86.9%, or 53) of our patients had a history of epilepsy. The mean age at presentation was 3.75 years (range: 0.8-17), with an SD of 0.81 years. Of the 53 patients, 31 were males and 22 were females. The most prevalent categories of seizures were generalised motor tonic-clonic (37.7%, n=23), mixed (36.1%, n=22), and epileptic spasms (32.8%, n=20) (**Table 6**).

The EEG was performed for 51 (83%) patients and found to be abnormal in 37 (60.7%) patients, with focal abnormalities being the most prevalent at 31.1% (n=19) (**Table 6**).

The EEG showed diffuse slowing of the background in some patients, while it showed focal and multifocal epileptiform discharges in others, with maximum

Table 1 - Patients' baseline characteristics.

Variables	Frequency (%)
Gender	
Male	36 (59.0)
Female	25 (41.0)
TSC type	
TSC 1	9 (14.8)
TSC 2	23 (37.7)
Untested genetically	29 (47.5)
Epilepsy	
Intractable epilepsy	28 (45.9)
Monotherapy	25 (40.9)
No epilepsy	8 (13.1)
Tuberous sclerosis associated neuropsychiatric disorders (TAND)	
Yes	45 (73.8)
No	16 (26.2)
Age	Mean (±SD)
Current age of participants	11.3±6.7
Age at diagnosis	4.9±4.9

SD - Standard deviation; TAND - Tuberous sclerosis associated neuropsychiatric disorders; TSC - Tuberous sclerosis complex

Table 2 - The distribution of the major diagnostic criteria across the study sample.

Criterias	n (%)
Major criteria	
Subependymal nodules (≥2)	53 (86.9)
Hypomelanotic Macules ((≥3; at least 5 mm diameter)	39 (63.9)
Multiple cortical tubers and//or radial migration lines	39 (63.9)
Angiomyolipoma (≥2)	24 (39.3)
Shagreen patch	16 (26.2)
Angiofibroma (≥3) or fibrous cephalic plaques	15 (24.6)
Cardiac rhabdomyoma	15 (24.6)
Multiple retinal hamartomas	13 (21.3)
Ungual fibromas (≥2)	1 (1.6)
Minor Criteria	
Multiple renal cysts	17 (27.9)
Confetti Skin Lesions	2 (3.3)
Sclerotic bones lesions	1 (1.6)
Intraoral fibromas	1 (1.6)
Non-renal hamartomas	1 (1.6)

Table 3 - The mean age at presentation of patients' diagnostic criteria.

Variables	Mean±SD
Non-renal hamartomas	1.0±0
Cardiac rhabdomyoma	1.6±2.8
Subependymal nodules	4.1±4.7
Multiple renal cysts	4.4±3.8
Confetti Skin Lesions	4.5±0.7
Multiple cortical tubers and//or radial migration lines	4.5±5.2
Hypomelanotic Macules	4.8±4.1
Intraoral fibromas	6.0±0
Subependymal Giant Cell Astrocytoma	6.7±6.3
Shagreen patch	6.8±4.4
Multiple retinal hamartomas	7.2±5.9
Angiomyolipoma	8.4±4.9
Angiofibroma or fibrous cephalic plaques	9.1±4.0
Dental Complications	9.8±4.8
Sclerotic bones lesions	11.0±0
Ungual fibromas	13.0±0

epileptiform discharges over the frontal and temporal head regions.

Epilepsy management was dominated by medical treatment. The majority of the patients (73.8% (n=45)) received ASMs, with levetiracetam (36.1%; n=22) and valproate (31.1%; n=19) being the most commonly used medications. Four patients with refractory seizures underwent surgery, three were treated with mTOR inhibitors, and one underwent VNS. No patients were treated with a ketogenic diet. **Table 6** displays the prevalence of the various epilepsy management strategies used by our participants.

Neuroimaging was performed on 93% (n=57) of our patients, of whom 91.8% (n=56) showed abnormalities. Moreover, 55.7% (n=43) of our patients were subjected to genetic testing. Of these, 14.8% (n=9) were diagnosed with TSC1, while 37.7% (n=23) were diagnosed with TSC2. Although males had a higher prevalence of TSC1 and TSC2, the difference was not statistically significant (p=0.613 and p=0.819, respectively).

The overall frequencies of TAND manifestations in the studied cohort are depicted in **Table 6**.

No significant difference was seen between the presence of TAND and gender. The TAND was present among 66.7% of those with TSC1 and 73.9% of those with TSC2.

In this study, 29.5% (n=18) of our cohort had cardiovascular manifestations, 9.8% (n=6) of which were arrhythmias. Mitral regurgitation was 3.3% (n=2), hypertension was 1.6% (n=1), and atrial septal defect was 1.6% (n=1). Only one patient (1.6%) with rhabdomyoma underwent cardiac surgery. **Table 6** outlines the treatment options available for TSC complications.

Discussion. In this study, the current mean age was 11 years, and the mean age at diagnosis was 4.9 years. In contrast, in a previously published study, Staley et al[26] noticed that the mean age at diagnosis was 7.5 years. This may reflect the progress made in the detection of TSC in recent years.

Almubarak et al[18] found that those who were genetically evaluated were more likely to carry TSC2 mutations than TSC1 mutations.[18] This mirrors the findings of our current investigation, where we identified that 14.8% of the patients were diagnosed

Table 4 - The distribution of tuberous sclerosis complex (TSC) features stratified by gender.

TSC Features	Male N (%)	Female N (%)	*P*-value
Hypomelanotic Macules	28 (77.8)	11 (44)	0.007*
Angiofibroma or fibrous cephalic plaques	10 (27.8)	5 (20)	0.488
Ungual fibromas	0 (0)	1 (4)	0.226
Shagreen patch	11 (30.6)	5 (20)	0.357
Multiple retinal hamartomas	8 (22.2)	5 (20)	0.835
Multiple cortical tubers and//or radial migration lines	22 (61.1)	17 (68)	0.582
Subependymal nodules	29 (80.6)	24 (96)	0.079
Subependymal Giant Cell Astrocytoma	7 (19.4)	7 (28)	0.435
Cardiac rhabdomyoma	10 (27.8)	5 (20)	0.488
Angiomyolipoma	15 (41.7)	9 (36)	0.656
Confetti Skin Lesion	2 (5.6)	0 (0)	0.231
Dental Complications	7 (19.4)	4 (16)	0.731
Intraoral fibromas	0 (0)	1 (4)	0.226
Multiple renal cysts	11 (30.6)	6 (24)	0.574
Non-renal hamartomas	1 (2.8)	0 (0)	0.401
Sclerotic bones lesions	1 (2.8)	0 (0)	0.401

Table 5 - The presentation of tuberous sclerosis complex (TSC) features stratified by gender.

TSC Features	Male Mean±SD	Female Mean±SD	*P*-value
Hypomelanotic Macules	4.9±4.2	4.7±4.1	0.888
Angiofibroma or fibrous cephalic plaques	8.2±4.3	10.8±3	0.266
Shagreen patch	7±4.5	6.4±4.5	0.800
Multiple retinal hamartomas	6±5.3	9±6.9	0.391
Multiple cortical tubers and/or radial migration lines	2.7±3	6.7±6.6	0.017*
Subependymal nodules	3.2±3.3	5.2±5.8	0.138
Subependymal Giant Cell Astrocytoma	6.2±4.9	7.2±7.9	0.798
Cardiac rhabdomyoma	2±3.4	0.8±1.1	0.469
Angiomyolipoma	8.2±4.4	8.8±5.8	0.758
Dental Complications	10±4.7	9.2±5.7	0.785
Multiple renal cysts	4.4±3.1	4.5±5.1	0.985
Seizure	4±3.9	3.3±4.4	0.510

with TSC1, while 37.7% were diagnosed with TSC2. This demonstrates that the Saudi population matches what has been reported in the literature. One of the initial symptoms of TSC is epilepsy, which manifests primarily as epileptic spasms. According to the 2012 International Tuberous Sclerosis Complex Consensus Group, approximately 85% of TSC patients are affected by this.[7] This was aligning with the findings of our study, where we identified that 86.9% of our patients had a history of epilepsy.

Despite epilepsy being one of the earliest manifestations of TSC, nearly 19% of patients were treated for it for 6 weeks to 36 years before receiving a formal diagnosis of TSC.[26] However, the prevalence of epilepsy among TSC patients remains variable, as Almubarak et al. have reported lower rates.[18] In both investigations, motor tonic-clonic seizure was found to be the predominant seizure semiology, affecting 37% of both cohorts. In contrast to the study of Almubarak et al[18] in which the rate of epileptic spasms was 15.9%, a higher rate of 32.8% was observed in our study.

The identification of epileptic spasms is crucial, and prompt treatment is essential as the cognitive prognosis is poor.[27] The majority of TSC-related epilepsy patients are resistant to treatment with standard ASMs and require multiple therapies management. Lamotrigine

Table 6 - The distribution of seizure types, TAND manifestations, and electroencephalography findings and epilepsy and TSC complications management profile across the study sample.

Variables	n (%)
Seizure Type	
Generalized motor tonic-clonic seizure	23 (37.7)
Mixed seizure	22 (36.1)
Epileptic spasms	20 (32.8)
Focal motor	19 (31.1)
Unclassified seizure type	14 (23.0)
Absence seizure	9 (14.8)
Lennox Gastaut	3 (4.9)
Juvenile myoclonic epilepsy	1 (1.6)
Other	7 (11.5)
TAND manifestations	
Learning disability	32 (52.5)
Speech delay	28 (45.9)
Intellectual disability	27 (44.3)
Global developmental delay	26 (42.6)
Social/ cognitive delay	25 (41.0)
Fine motor delay	11 (18.0)
ASD	11 (18.0)
Gross motor delay	10 (16.4)
ADHD	9 (14.8)
Electroencephalography findings	
Focal abnormality	19 (31.1)
Focal frontal epileptiform discharges	12 (19.7)
Focal temporal epileptiform discharges	12 (19.7)
Focal parietal epileptiform discharges	3 (4.9)
Focal occipital epileptiform discharges	8 (13.1)
Generalized slow abnormality	8 (13.1)
Other EEG finding	7 (11.3)
Generalizes spike/wave epileptiform discharges	6 (9.8)
3 Hz Spike wave discharges	1 (1.6)
Epilepsy management profile	
Anti-seizure medication	45 (73.8)
Single anti-seizure medication	18 (29.5)
Two or more anti-seizure medication	27 (44.3)
Surgery for Seizure	4 (6.5)
SEGA surgery	3 (4.9)
mTOR inhibitors	3 (4.9)
Vagus nerve stimulation	1 (1.6)
Management of TSC complications	
Surgery for Seizure	4 (6.5)
Cardiac rhabdomyoma surgery	1 (1.6)
Multiple retinal astrocytoma surgery	1 (1.6)
Renal transplant	1 (1.6)
V-P shunt insertion	1 (1.6)

(34.7%), valproate (32.8%), oxcarbazepine (28.9%), vigabatrin (19.0%), and levetiracetam (17.9%) were the ASMs most commonly used in the German population, according to a study.[28] In comparison to our sample, levetiracetam was the most commonly used ASM at 36.1%, followed by valproate at 31.0%.

Neurocutaneous stigmata are essential for the diagnosis of TSC, and a comprehensive clinical dermatological examination is essential, as they constitute four major and 3 minor criteria. Although they appear early on, the onset of these cutaneous characteristics varies depending on age and gender. In our study, hypomelanotic macules were significantly more prevalent in males compared to females, accounting for 77.8% and 44%, respectively (p=0.007). Similar to our findings, hypomelanotic macules have been reported to affect more than 90% of TSC patients in many large studies.[29] In addition, the advent of the other cutaneous manifestations was consistent with the literature, albeit at a lower frequency than anticipated. This was likewise noted in the article by Almubarak et al.[18] Approximately half of TSC patients are afflicted by shagreen regions, according to one study.[30] In the current investigation and the study by Almubarak et al[18] the prevalence of shagreen regions was 26.2% and 13.6%, respectively.[18]

Lesions of angiofibroma progress with advancing age. Approximately 8% of TSC patients younger than 2 years old exhibit angiofibroma, compared to 75% of those older than nine years.[31] Around 24.6% of our cohort was initially diagnosed with angiofibroma at an average age of 9 years. Consistent with what Almubarak et al[18] reported, only one patient in our study manifested with ungual fibroma.

The most burdensome aspect of TSC is its association with neuropsychiatric conditions. In our study, we did not identify any statistically significant difference between males and females in terms of the prevalence of TAND. This was consistent with the findings of a previous study that examined the prevalence of TAND among the pediatric population, which showed comparable findings.[33] A study of TAND revealed that 88% of patients with TSC were affected by at least one TAND entity, while 78% had more than four TAND entities.[34] In addition, the earlier the onset of seizures in TSC patients, the greater the likelihood that the patient will develop multiple neuropsychiatric disorders. The mutation in TSC2 was associated with a higher incidence of intellectual disability and autism spectrum disorders.[35,36] Epilepsy, epileptic spasms, and TSC2 mutations were risk factors for the development of ASD in TSC patients, according to one study.[21] TAND was detected in 66.7%, 73.9%, and 67.6% of TSC1 patients, TSC2 patients, and DRE patients, respectively. One study supported the applicability of a

TAND detection protocol in TSC patients.[37] Therefore, the use of screening tools is necessary to guarantee a prompt diagnosis of TAND and, consequently, an improved prognosis for the disease.

Cardiac rhabdomyomas are strongly linked to TSC. Although benign, if sufficiently large, these hamartomatous lesions can cause significant mass effects, resulting in arrhythmia and cardiac failure.[38] In our study, cardiac rhabdomyomas were observed in 15 patients, or approximately 25%. Six of these 15 patients developed cardiac arrhythmias due to the lesions. The mean age of diagnosis for these cardiac lesions was 1.6±2.8 years, making it the earliest clinical manifestation of TSC among our participants. Although cardiac rhabdomyomas are an early finding in TSC, they typically regress spontaneously in the early stages of the disease. Compared to our findings, the prevalence of cardiac rhabdomyomas in TSC patients is higher in other studies.[39,40] The age at which TSC was diagnosed in our participants may be one plausible explanation for this lower prevalence. In addition, the fact that not all of our asymptomatic patients have undergone an echocardiogram is a potential explanation for this decreased prevalence. In contrast to other clinical manifestations of TSC, these cardiac lesions are detectable in utero.[38] Patients with cardiac rhabdomyoma require echocardiogram and electrocardiogram monitoring for early detection of complications, including electrical disturbances, as observed in 6 of our patients.[41]

Renal manifestations are prevalent among TSC patients and are regarded as a major cause of morbidity and mortality.[42] In our study, the prevalence of AMLs (39.3%) exceeded that of multiple renal cysts (27.9%). This is consistent with the results of other investigations of a similar nature.[39,42] Renal AMLs are associated with renal dysfunction and impairment. Around 16% of TSC patients with AMLs who were observed for 12 years by a cohort study developed Stage 3 or higher chronic kidney disease (CKD).[43] This decline in renal function due to AMLs was observed in one of the patients who developed Stage 5 CKD in our study. This emphasises the need for vigilant surveillance of renal function in TSC patients.

To achieve optimal results, TSC administration necessitates the incorporation of numerous specialities. The complexity of TSC necessitates a multidisciplinary team (MDT) approach. This improves the outcome by ensuring that all specialists are efficiently interconnected. In addition, the MDT approach would facilitate the transition from adolescent to adult care. Existing gaps in the literature necessitate additional research on the establishment of TSC multidisciplinary team plans and guidelines with an emphasis on the role of each specialist.

Our study has certain limitations. First, this is a retrospective study based on a review of patient records. The original intent of these infographics was not data collection. Therefore, information may be lacking or inadequately documented. Second, cutaneous and dental manifestations may have been underreported because not all of our patients underwent comprehensive dental and dermatological examinations. Our study also included TSC patients from a single centre, which is NGHA. One potential bias that may arise among patients is related to the specificity of the NGHA facility. This bias stems from the fact that patients who are linked to the Saudi Arabian National Guard and their relatives often have priority access to NGHA facilities. This may result in disparities in healthcare access when compared to the broader population. Moreover, the distinctiveness of NGHA services may result in patients obtaining exceptionally specialized care, hence offering advantages to individuals with specific medical needs in those particular domains. Therefore, our findings should be interpreted carefully.

Conclusion. The TSC is a medical condition characterized by a range of neurological, cutaneous, and radiological manifestations. Males were substantially more likely than females to have hypomelanotic macules. Furthermore, it was shown that males had a notable development of cortical tubers and/or radial migration lines at an earlier stage compared to females. Almost half of the sample was subjected to genetic testing, which revealed a higher prevalence of TSC2. Neuropsychiatric disorders and a history of epilepsy were documented in the majority of our patients, and nearly half of those with epilepsy had intractable epilepsy.

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References

1. O'Callaghan FJ, Shiell AW, Osborne JP, Martyn N. Prevalence of tuberous sclerosis estimated by capture-recapture analysis. ***Lancet (London, England)*** 1998; 351: 1490.
2. Tee AR, Sampson JR, Pal DK, Bateman JM. The role of mTOR signalling in neurogenesis, insights from tuberous sclerosis complex. ***Semin Cell Dev Biol*** 2016; 52: 12-20.
3. Yates JR, Maclean C, Higgins JN, Humphrey A, le Maréchal K, Clifford M, et al. Tuberous Sclerosis 2000 Study Group. The Tuberous Sclerosis 2000 Study: presentation, initial assessments and implications for diagnosis and management. ***Arch Dis Child*** 2011; 96: 1020-1025.

4. Jones AC, Shyamsundar MM, Thomas MW, Maynard, J, Idziaszczyk S, Tomkins S, et al. Comprehensive mutation analysis of TSC1 and TSC2-and phenotypic correlations in 150 families with tuberous sclerosis. ***Am J Hum Genet*** 1999; 64: 1305-1315.
5. Sancak O, Nellist M, Goedbloed M, Elfferich P, Wouters C, Maat-Kievit A, et al. Mutational analysis of the TSC1 and TSC2 genes in a diagnostic setting: genotype--phenotype correlations and comparison of diagnostic DNA techniques in Tuberous Sclerosis Complex. ***Eur J Hum Genet*** 2005; 13: 731-741.
6. Tyburczy ME, Dies KA, Glass J, Camposano S, Chekaluk Y, Thorner AR, et al. Mosaic and Intronic Mutations in TSC1/TSC2 Explain the Majority of TSC Patients with No Mutation Identified by Conventional Testing. ***PLoS genetics.*** 2015; 11: 1-17.
7. Northrup H, Aronow ME, Bebin EM, Bissler J, Darling TN, de Vries, PJ, et al. International Tuberous Sclerosis Complex Consensus Group. Updated International Tuberous Sclerosis Complex Diagnostic Criteria and Surveillance and Management Recommendations. ***Pediatr Neurol*** 2021; 123: 50-66.
8. Peron A, Northrup H. Tuberous sclerosis complex. ***Am J Med Genet C Semin Med Genet*** 2018; 178: 274-277.
9. Bader RS, Chitayat D, Kelly E, Ryan G, Smallhorn JF, Toi A, et al. Fetal rhabdomyoma: prenatal diagnosis, clinical outcome, and incidence of associated tuberous sclerosis complex. ***J Pediatr*** 2003; 143: 620-624.
10. Northrup H, Krueger DA, International Tuberous Sclerosis Complex Consensus Group. Tuberous sclerosis complex diagnostic criteria update: recommendations of the 2012 Iinternational Tuberous Sclerosis Complex Consensus Conference. ***Pediatric neurology*** 2013; 49: 243-254.
11. Adriaensen ME, Schaefer-Prokop CM, Duyndam, DA, Zonnenberg BA, Prokop M. Radiological evidence of lymphangioleiomyomatosis in female and male patients with tuberous sclerosis complex. ***Clin Radiol*** 2011; 66: 625-628.
12. Au KS, Williams AT, Roach ES, Batchelor L, Sparagana SP, Delgado MR, et al. Genotype/phenotype correlation in 325 individuals referred for a diagnosis of tuberous sclerosis complex in the United States. ***Genet Med*** 2007; 9: 88-100.
13. Numis AL, Major P, Montenegro MA, Muzykewicz DA, Pulsifer MB, Thiele EA. Identification of risk factors for autism spectrum disorders in tuberous sclerosis complex. ***Neurology*** 2011; 76: 981-987.
14. Yang P, Cornejo KM, Sadow PM, Cheng L, Wang M, Xiao Y, et al. Renal cell carcinoma in tuberous sclerosis complex. ***Am J Surg Pathol*** 2014; 38: 895-909.
15. Holmes GL, Stafstrom CE. Tuberous Sclerosis Study Group. Tuberous sclerosis complex and epilepsy: recent developments and future challenges. ***Epilepsia.*** 2007; 48: 617-630.
16. Nabbout R, Belousova E, Benedik MP, Carter T, Cottin V, Curatolo P, et al. TOSCA Consortium and TOSCA Investigators. Epilepsy in tuberous sclerosis complex: Findings from the TOSCA Study. ***Epilepsia open*** 2018; 4: 73-84.
17. Sparagana SP, Delgado MR, Batchelor LL, Roach ES. Seizure remission and antiepileptic drug discontinuation in children with tuberous sclerosis complex. ***Arch Neurol*** 2003; 60: 1286-1289.
18. Almobarak S, Almuhaizea M, Abukhaled M, Alyamani S, Dabbagh O, Chedrawi A, et al. Tuberous Sclerosis Complex: Clinical Spectrum and Epilepsy: A Retrospective Chart Review Study. ***Transl Neurosci*** 2018: 9: 154-160.
19. de Vries PJ, Whittemore VH, Leclezio L, Byars AW, Dunn D, Ess KC, et al. Tuberous sclerosis associated neuropsychiatric disorders (TAND) and the TAND Checklist. ***Pediatr Neurol*** 2015; 52: 25-35.
20. Smalley SL. Autism and tuberous sclerosis. ***J Autism Dev Disord*** 1998; 28: 407-414.
21. Vignoli A, La Briola F, Peron A, Turner K, Vannicola C, Saccani M, et al. Autism spectrum disorder in tuberous sclerosis complex: searching for risk markers. ***Orphanet J Rare Dis*** 2015; 10: 1-9.
22. Alsowat D, Zak M, McCoy B, Kabir N, Al-Mehmadi S, Chan V, et al. A Review of Investigations for Patients With Tuberous Sclerosis Complex Who Were Referred to the Tuberous Sclerosis Clinic at The Hospital for Sick Children: Identifying Gaps in Surveillance. ***Pediatr Neurol*** 2020: 102: 44-48.
23. Wiznitzer M. Autism and tuberous sclerosis. ***J Child Neurol*** 2004; 19: 675-679.
24. Jackson GD, Kuzniecky RI, Berkovic SF. CHAPTER 1 - Introduction to Epilepsy. In: Kuzniecky RI, Jackson GD, editors. Magnetic Resonance in Epilepsy. Second Edition. Burlington: Academic Press; 2005:1-16.
25. Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Allen Hauser W, Mathern G, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. ***Epilepsia*** 2010; 51: 1069-1077.
26. Staley BA, Vail EA, Thiele EA. Tuberous sclerosis complex: diagnostic challenges, presenting symptoms, and commonly missed signs. ***Pediatrics*** 2011; 127: e117-e125.
27. Goh S, Kwiatkowski DJ, Dorer DJ, Thiele EA. Infantile spasms and intellectual outcomes in children with tuberous sclerosis complex. ***Neurology*** 2005; 65: 235-238.
28. Schubert-Bast S, Strzelczyk A. Review of the treatment options for epilepsy in tuberous sclerosis complex: towards precision medicine. ***Ther Adv Neurol Disord*** 2021; 14: 1-22.
29. Jacks SK, Witman PM. Tuberous Sclerosis Complex: An Update for Dermatologists. ***Pediatr Dermatol*** 2015; 32: 563-570.
30. Cardis MA, DeKlotz CM. Cutaneous manifestations of tuberous sclerosis complex and the paediatrician's role. ***Archives of disease in childhood*** 2017; 102: 858-863.
31. Cascarino M, Leclerc-Mercier S. Histological Patterns of Skin Lesions in Tuberous Sclerosis Complex: A Panorama. ***Dermatopathology (Basel)*** 2021; 8: 236-252.
32. Shalabi D, Sethi M, Lee H, Cha J, Nikbakht N. Diagnosis of Tuberous Sclerosis Complex in Adulthood based on Late Presenting Cutaneous Manifestations. ***J Fam Med*** 2019; 6: 1-3.
33. Ding Y, Wang J, Zhou H, Li T, Zhou S, Wang Y. Assessment of tuberous sclerosis-associated neuropsychiatric disorders using the MINI-KID tool: a pediatric case-control study. ***Orphanet J Rare Dis*** 2021; 16: 181.
34. Toldo I, Brasson V, Miscioscia M, Pelizza MF, Manara R, Sartori S, et al. Tuberous sclerosis-associated neuropsychiatric disorders: a paediatric cohort study. ***Dev Med Child Neurol*** 2019; 61: 168-173.
35. Capal JK. Epilepsy and TSC-Associated Neuropsychiatric Disorders. ***Pediatr Neurol Briefs*** 2020; 34: 11.
36. Schoenberger A, Capal JK, Ondracek A, Horn PS, Murray D, Byars AW, et al. Language predictors of autism spectrum disorder in young children with tuberous sclerosis complex. ***Epilepsy Behav*** 2020; 103: 1-20.
37. Cervi F, Saletti V, Turner K, Peron A, Bulgheroni S, Taddei M, et al. The TAND checklist: a useful screening tool in children with tuberous sclerosis and neurofibromatosis type 1. ***Orphanet journal of rare diseases*** 2020; 15: 1-11.

38. Frudit P, Vitturi BK, Navarro FC, Rondelli I, Pozzan G. Multiple cardiac rhabdomyomas in tuberous sclerosis complex: case report and review of the literature. ***Autops Case Rep*** 2019; 9: e2019125
39. Barzegar M, Poorshiri B, Yousefi L, Raeisi S, Bakhtiary H, Eftekhari Milani A, et al. The clinical and paraclinical manifestations of tuberous sclerosis complex in children. ***Acta neurologica Belgica*** 2022; 122: 385-390.
40. Hinton RB, Prakash A, Romp RL, Krueger DA, Knilans T, International Tuberous Sclerosis Consensus Group. Cardiovascular manifestations of tuberous sclerosis complex and summary of the revised diagnostic criteria and surveillance and management recommendations from the International Tuberous Sclerosis Consensus Group. ***J Am Heart Assoc*** 2014; 3: 1-11.
41. Shiono J, Horigome H, Yasui S, Miyamoto T, Takahashi-Igari M, Iwasaki N. Electrocardiographic changes in patients with cardiac rhabdomyomas associated with tuberous sclerosis. ***Cardiol Young*** 2003; 13: 258-263.
42. Nair N, Chakraborty R, Mahajan Z, Sharma A, Sethi SK, Raina R. Renal Manifestations of Tuberous Sclerosis Complex. ***J Kidney Cancer VHL*** 2020; 7: 5-19.
43. Seyam RM, Alkhudair WK, Kattan SA, Alotaibi MF, Alzahrani HM, Altaweel WM. The Risks of Renal Angiomyolipoma: Reviewing the Evidence. ***J Kidney Cancer VHL*** 2017; 4: 13-25.