Central nervous system manifestations of tuberous sclerosis complex

A single centre experience in Qatar

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ABSTRACT

الأهداف: لمراجعة الارتباط بين الجانب السريري و الجانب الإشعاعي لمظاهر إصابة الجهاز العصبي المركزي بمرض التصلب الدرني.

المنهجية: تم تضمين جميع المرضى الذين تقل أعمارهم عن 18 عامًا والذين تم تشخيصهم بمرض التصلب الدرني والذين تمت متابعتهم في مؤسستنا بين يناير 2003 و فبراير 2021 في هذه الدراسة التي تمت بأثر رجعي و استخدمت أداة E-CHESS (درجة شدة الصرع في مرحلة الطفولة المبكرة) لتحديد شدة الصرع.

النتائج: شملت عينة الدراسة 38 مريضًا (50% منهم من الذكور) حيث كان 8 مرضى (21%) من مواطني قطر و 24 مريضًا (63%) تم تشخيصهم في قطر. كان متوسط العمر عند التشخيص أربعة أشهر (النطاق= 0-72 شهرًا). بالرغم من أن التاريخ العائلي للمرض كان ايجابياً في 10 حالات فقط (26%) إلا أن لدى 33 مريضًا (86%) طفرة في جين *TSC2*. الأعراض المرضية التي ظهرت عند مرضى الدراسة شملت النوبات الصرعية (79%)، ورم عضلة القلب (26%)، والتأخر في النمو (13%). في فحوصات التصوير بالرنين المغناطيسي، كان لدى جميع المرضى درنات قشرية، وشوهدت عقيدات تحت البطانة العصبية في 37 مريضًا (97%) وتم تشخيص ورم الخلايا النجمية العملاقة تحت البطانة العصبية في 8 حالات (21%). تم تشخيص ثلاثين طفلاً بالصرع، كان لدى 9 منهم درجات ذات أفضلية و21 درجات ليس لها أفضلية في اختبار E-CHESS، و تطلب الأمر علاج 6 منهم بالأدوية. بالإضافة إلى ذلك، تم تشخيص 13 طفلاً باضطراب طيف التوحد و12 طفلاً باضطراب نقص الانتباه وفرط النشاط.

الخلاصة: نظرًا لأن مرض التصلب الدرني هو تشخيص مرهق لمعظم الأفراد المتضررين وأسرهم، فإن المتابعة و العلاج من جميع المختصين في هذا المرض مطلوبة لضمان جودة حياة جيدة. هناك حاجة إلى مزيد من الأبحاث لتحسين التعامل الطبي مع المرض.

Objectives: To review the clinical and radiological correlation of the central nervous system manifestations of tuberous sclerosis complex (TSC).

Methods: All patients under the age of 18 years with TSC seen at the Department of Pediatrics, Sidra Medicine, Doha, Qatar, between January 2003 and February 2021 were included in this retrospective study. Severity of epilepsy was determined using the early childhood epilepsy severity score (E-CHESS) tool.

Results: The study sample included 38 patients (50% male), 8 (21%) of whom were native to Qatar. The median age at diagnosis was 4 (range: 0-72) months. A family history of TSC was present in 10 (26%) cases, while 33 (86%) patients had a *TSC2* gene mutation. Common presentations included seizures (79%), rhabdomyoma (26%), and developmental delay (13%). On MRI scans, cortical tubers were seen in all patients, subependymal nodules in 37 (97%), and subependymal giant cell astrocytoma was diagnosed in 8 (21%) cases. A total of 30 children developed epilepsy, 9 of whom had favorable and 21 had unfavorable E-CHESS scores, and 6 required pharmaceutical management. A total of 13 children were diagnosed with autistic spectrum disorder and 12 with attention deficit hyperactivity disorder.

Conclusion: Multidisciplinary management and further research is needed to optimize the care and quality of life of TSC affected individuals and their families.

Keywords: epilepsy, infantile spasms, subependymal nodules, SEGA, TAND

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Tuberous sclerosis complex (TSC) is a rare, genetic disorder present in 1 in 6,000 to 1 in 10,000 live births, with an estimated prevalence of 1 in 20,000.[1] It is inherited in an autosomal dominant manner in approximately one third of those affected, and as the result of a de novo mutation in the remaining cases. There is a wide variation in presentation among individuals belonging to different families or even within the same family.[2] Central nervous system (CNS), skin, heart and kidneys bear the brunt of clinical manifestations of TSC.[3,4] All patients with TSC carry loss-of-function germline mutations in either of the 2 tumor-suppressor genes, *TSC1* which encode for the protein hamartin or *TSC2* which encode for the protein tuberin.[5] These proteins regulate cell proliferation and differentiation, the loss of which can lead to the abnormal development and generation of cells through faulty, inefficient, or the absent protein products. Accordingly, mutations in either the *TSC1* or *TSC2* gene lead to hyperactivation of the mechanistic target of rapamycin (mTOR) pathway, which is a signaling cascade that modulates a variation of intracellular function including cell growth and proliferation, protein synthesis, and metabolism. Hyperactivation of this pathway leads to growth dysregulation that ultimately results in clinical manifestations of TSC.[4]

Epilepsy and developmental delay are the most well-recognized features of TSC. An ensemble of neuropsychiatric manifestations experienced by TSC patients is known as TSC associated neuropsychiatric disorders (TAND) which includes behavioural, intellectual, neuropsychiatric, academic and psychosocial difficulties.[6] It also includes specific conditions such as autistic spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD). An attractive mechanism of pathophysiology of TAND, in common with other manifestations of TSC, is provided by mTOR dysregulation. Early reports of neuropsychiatric response with the use of mTOR inhibitor therapy support this hypothesis.[7]

Neuroradiological features of TSC include cortical/subcortical hamartomas (tubers) and subependymal nodules (SENs) in over 80% of patients.[8] Subependymal nodules were found in the ependymal lining of the lateral and third ventricles. They grow at variable pace throughout childhood, usually peaking around puberty.[9] In approximately 10-15% of cases, those present around the foramen of Monro have a higher likelihood of developing into subependymal giant cell astrocytomas (SEGAs).[9,10] Cortical tubers and SENs have long been considered the epileptogenic focus in TSC patients. Further understanding of the TSC neurobiology has led to the recognition of the peritubeal cortex as epileptogenic foci through cellular dysplasia and mTOR signalling.[11]

Qatar is a high-income developing country populated by 3.1 million people. Only 10-11% of the population are native to Qatar, while the remaining 89-90% are expatriates. Approximately 32.5% of Qatari children are within the 0-14 age group.[12,13] Comprehensive healthcare is delivered to the entire population through the Qatar National Health Services via government funds and employer-issued insurance system. Per capita healthcare resources (physician and hospital beds) are within the highest in the region and are similar to those in most developed countries.[14] The population is mostly urbanized with highly accessible healthcare facilities including neuroradiologic facilities. Currently, the management of TSC patients is carried out by a core team of physicians from clinical genetics, pediatric neurology, oncology, and nephrology, who carry out the diagnostic evaluation, surveillance, and treatment where necessary. Referral to other specialists/teams is carried out based on patients' individual needs.

This retrospective cohort study was carried out by our team to examine the presentation, neurological, and radiological features of TSC.

Methods. We retrospectively reviewed electronic medical records at Sidra Medicine and Hamad General Hospital, Doha, Qatar. Data of patients 0-18 years old who were referred to pediatric neurology for TSC evaluation between January 2003 and February 2021 were included in the sample used for analyses. The study protocol was approved by the institutional review board of Sidra Medicine (IRB No.: 1500797).

We used the standardized diagnostic criteria as indicated by the 2012 International Tuberous Sclerosis Complex Consensus Conference for TSC.[3] Patients who did not fit the criteria for TSC were excluded from analysis while the remaining patients underwent genetic assessment, which involved a detailed family history and pedigree analysis, as well as blood testing for the *TSC1* and *TSC2* genes at accredited commercial laboratories. Their electronic medical records were also analyzed and data pertaining to gender, age at TSC diagnosis, familial history of TSC, developmental milestones, presence and type (and age of first presentation) of epilepsy, presence of tubers, SEN and SEGA on neuroimaging, and neurological examination findings at last follow-up were recorded. Subependymal giant cell astrocytoma diagnosis was based on size, location, and behavior over time. Lesions close to the foramen of Monro, causing or likely to cause obstruction, exceeding 5 mm in diameter

(or demonstrating an increase in size by 5 mm) were considered SEGA, whereas smaller, non-obstructive lesions were denoted as SENs.

The epilepsy severity and response to therapy was assessed by using the early childhood epilepsy severity score (E-CHESS).[15] According to the most recent documented evaluation, a note was made of the period of seizure occurrence, frequency, count of seizure types, status epilepticus occurrence and duration, amount of anticonvulsant medications used, and response to treatment.

The TAND checklist (developed by the Neuropsychiatry Panel at the 2012 Tuberous Sclerosis Complex International Consensus Conference, as reported by de Vries et al[6]) was used to record the manifestations. The assessment was carried out at the behavioral, intellectual, neuropsychological, psychiatric, academic, and psychosocial levels. Families were interviewed and feedback to the TAND questionnaire were recorded by the specialized clinical nurse after the child's follow-up appointments at the hospital or over the telephone at a mutually convenient time.

Statistical analysis. Patient and disease attributes are expressed in numerical and percentage form per attribute. Standard statistical tests were carried out to calculate numbers, percentages, and median values. The Statistical Package for the Social Sciences, version 25.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis.

Results. As shown in Table 1, providing a summary of patient and disease characteristics, the final analysis involved 38 patients with TSC as 4 children did not fulfill the diagnostic criteria for TSC. Median age at diagnosis for the remaining cohort was 4 (range: 0-72) months. A total of 8 (21%) children were native to Qatar, and the remaining 30 were expatriates. In 24 (63%) cases, the TSC diagnosis was carried out in Qatar, whereas the remaining 14 patients had already been diagnosed elsewhere before relocating to Qatar. Family history of TSC were seen in 10 (26.3%) patients.

Epileptiform seizures were the predominant presenting feature, and were present in 30 (79%) cases, including infantile spasms, affecting 14 (37%) of these children. This was followed by cardiac rhabdomyoma (RM, n=8, 26%), developmental delay/learning disability (4 cases, 13%), and hypopigmented spots (4 cases, 13%). As indicated in Table 1, at least 2 major diagnostic criteria were present in all patients, including hypomelanotic skin lesions (76%) and angiofibroma (52%), SEN (97%), cortical dysplasia (76%), SEGA (26%), multiple renal cysts (76%), and cardiac RM.

Table 1 - Patients and disease characteristics (N=38).

Characteristics	n (%)
Gender	
Male	19 (50.0)
Female	19 (50.0)
Age at diagnosis, median (range)	4 (0-72)
Age group	
Up to 4 months	20 (52.6)
4-12 months	14 (36.8)
Over 12 months	4 (10.5)
Diagnosis	
Qatar	24 (63.1)
Elsewhere	14 (36.9)
Family history	
Yes	10 (26.3)
No	28 (73.7)
Genetic analysis	
Mutation in TSC1	1 (2.6)
Mutation in TSC2	33 (86.8)
Genetic studies negative	4 (10.5)
Presentation	
Infantile spasms	14 (36.8)
Seizures (other than infantile spasms)	18 (47.3)
Developmental delay	5 (13.1)
Cardiac rhabdomyoma	8 (21.0)
Hypopigmented spots	5 (13.1)
Major criteria for TSC	
Hypomelanotic nodules	29 (76.3)
Angiofibroma	20 (52.6)
Ungual fibroma	0 (0.0))
Shagreen patch	7 (18.4)
Retinal hamartoma	5 (13.1)
Cortical dysplasia	29 (76.3)
Subependymal nodules	37 (97.3)
SEGA	10 (26.3)
Cardiac rhabdomyoma	16 (42.1)
LAM	0 (0.0)
AML	22 (57.8)
Minor criteria for TSC	
Confetti lesions	4 (10.5)
Dental enamel pits	2 (5.3)
Intra-oral fibroma	2 (5.3)
Retinal achromic patch	0 (0.0)
Multiple renal cysts	29 (76.3)
Non-renal hamartomas	4 (10.5)
Neuro-imaging features	
Tubers	37 (97.3)
SEN	37 (97.3)
SEGA	10 (26.3)

Values are presented as numbers and percentages (%).
TSC: tuberous sclerosis complex, SEGA: subependymal giant cell astrocytoma, LAM: lymphangioleiomyomatosis, AML: angiomyolipoma, SEN: subependymal nodules

The *TSC1* and *TSC2* gene mutation analyses revealed that 33 (87%) individuals had an alteration in the *TSC2* gene, while only one patient had a *TSC1* gene mutation, and the remaining 4 (10%) patients had negative genetic results (Tables 1 & 2).

A total of 32 (84.2%) patients had at least one seizure, 30 (78.9%) of whom were diagnosed with epilepsy. At the most recent evaluation, 6 (20%) patients were experiencing daily seizures, 10 (33%) had seizures at least once a week, while the remaining 14 (46%) had less frequent or no seizures during the evaluation period. A total of 25 (65.8%) individuals had one seizure type, the most common form being infantile spasms (IS) seen in 14 (46.6%) patients, followed by tonic-clonic seizures (12 cases, 40%). Complete cessation of seizures was achieved in 19 (63%) patients and partial cessation of seizures was achieved in 8 (21.1%) patients, while 3 (10%) patients showed no response to anticonvulsive therapy. A total of 15 (50%) patients were given 1-2 anti-epileptic drugs (AEDs), whereas 12 (40%) required more than 2 AEDs. Three patients were no longer receiving AED treatment by the last evaluation, while 2 patients undergone epilepsy surgery with effective epilepsy control (albeit with AED). Valproate and clobazam (13 patients each) were the 2 most frequently used AEDs, followed by vigabatrin (10), levetiracetam (8), topiramate (6), carbamazepine (4), lacosamide (2), clonidine (2) and ethosuximide (1). Vigabatrin was the AED of choice for patients with infantile spasms (10). Nine (27%) patients had a favorable E-CHESS score, which was unfavorable in 21 (73%) cases. Table 2 and 3 summarized these findings.

In our cohort, the TSC neuroimaging features included tubers (97.3%), SENs (97.3%), and SEGA (26.3%). Although tubers were distributed throughout the cerebral hemispheres, the frontal lobes were the most commonly involved region (seen in 8/38 patients, 21%). Six (15%) patients had a cerebellar tuber in addition to the supratentorial lesions. Subependymal nodules were distributed around the ependymal lining of lateral ventricles, and were labeled as SEGA in 8 (21%) cases due to their location and size. Five (62.5%) patients with SEGA received mTOR inhibitor therapy due to an increase in SEGA size and current or impending obstruction to the cerebrospinal fluid (CSF) flow. After a median follow-up period of 56 (range: 0-101) months, 2 of these lesions showed clinically significant progression requiring surgical management, 2 showed radiological regression within one year of starting treatment mTOR inhibitor everolimus, while the remaining 4 remained stable over the follow-up period. One patient requiring surgical resection continued receiving everolimus treatment with stable residual SEGA, while the other had a postoperative cerebrovascular accident (CVA). In the latter case, everolimus was withheld after surgical excision and the residual SEGA subsequently remained stable. No progression was seen in any of the other patients treated with everolimus. Summaries of these findings can be found in **Tables 2 & 3**.

As shown in **Table 4**, at least one TAND feature was observed in 32 (84%) patients, while more than 4 TAND features were seen in 27 patients. At the behavioral level, the most common TAND manifestations were poor language development (72%), poor attention span (62%), and poor eye contact (44%). Psychiatrically, ASD (42%) and ADHD (24%) were the 2 most frequently observed features. At the academic level, 69% of children experienced difficulties in writing and spelling, while 65% each had difficulties in reading and mathematics. At the neuropsychological level, 51% of children had problems with memory, 41% with multitasking, 38% with visuospatial tasks, and 34% with cognitive flexibility. Finally, at the psychosocial level, family stress was observed in 31% of cases.

Discussion. Several researchers from the Gulf region have published reports on various aspects of TSC in recent years.[16] The median age of 4 months at diagnosis in our cohort is lower than previously reported, likely due to available genetic screening and diagnosis of RM on antenatal maternal scans.[17] In addition, Qatar's small population and ready access to specialist services may play a role in early diagnosis.

The frequencies of sporadic and familial cases were the same as reported previously. We also found higher incidence of *TSC2* gene mutations, which is consistent with the findings yielded by many previous studies. A higher prevalence of *TSC2* mutations compared to *TSC1* has been reported by other researchers.[16,18] Mutations in the *TSC1* and *TSC2* genes are responsible for pathological constitutive activation of the highly conserved PI3K-mTOR pathway leading to the development of hamartomas (benign tumors) in various organs including the CNS.[3,19] In mice, homozygous loss of *TSC2* leads to embryonic lethality, while those with heterozygous *TSC2* have normal survival, but are prone to develop tumors in various organs including kidney, liver, and lungs.[20,21] The *TSC1* acts as stabilizer of *TSC2*, while *TSC2* in the complex acts as GTPase activating protein.[22] Clinically, *TSC1* mutations lead to a milder form of illness, while *TSC2* mutations are associated with high tuber count and severer form.[23] The high frequency of *TSC2* mutations in our cohort may thus be responsible for the severe clinical, radiological, and neuropsychiatric manifestations of the disease reported here.

The prevalence of epilepsy and the type of seizures observed in our patients were in line with those reported in pertinent literature, including a high

Table 2 - Presenting clinical and radiological features for all patients with tuberous sclerosis.

No.	Gender	Age at diagnosis (months)	Presentation	FH	Genetics	Epilepsy (E-CHESS score)	DD	LD	Tubers (dominant lobe)	Mineral-ization	SEN	SEGA
1.	M	1	Fits, RM	No	TSC2	Yes (7)	Yes	Yes	Yes (right temporal lobe)	Partial	Foramen of Monro (b/l)	Yes
2.	M	6	Fits	No	TSC2	Yes (8)	Yes	Yes	Yes (right Frontotemporal lobe)	No	Foramen of Monro (L)	Yes
3.	F	6	Fits, DD	No	TSC2	Yes (7)	Yes	Yes	Yes (none)	No	Frontal horn (R)	Yes
4.	F	4	IS, HS	No	TSC2	Yes (8)	Yes	Yes	Yes (both frontal lobes)	No	Foramen of Monro (b/l)	No
5.	M	3	Fits, LD	No	TSC2	Yes (7)	Yes	Yes	Yes (none)	Partial	Frontal horn (R)	Yes
6.	F	0		No	TSC2	No	No	No	Yes (both frontal lobes)	No	Foramen of Monro (R)	Yes
7.	M	11	IS	No	TSC2	Yes (11)	Yes	No	Yes (left temporoparietal lobes)	No	Lateral ventricles (b/l)	No
8.	M	0	IS	No	TSC2	No	No	No	Yes (none)	No	Foramen of Monro (R)	No
9.	M	1	RM	Yes	TSC2	Yes (7)	Yes	Yes	Yes (right Parieto-occipital lobe)	Partial	Foramen of Monro (L)	No
10.	M	7	IS	Yes	TSC2	Yes (8)	Yes	Yes	Yes (none)	Partial	Foramen of Monro (b/l)	No
11.	F	12	HS	Yes	TSC2	No	No	Yes	Yes (none)	No	Frontal horn (R)	No
12.	F	1	Fits	Yes	TSC2	Yes (8)	Yes	Yes	Yes (none)	Partial	Frontal horn (left)	No
13.	M	6	IIS	Yes	TSC2	Yes (9)	No	Yes	Yes (none)	Partial	Lateral ventricles (b/l)	No
14.	M	2	Fits	Yes	TSC2	Yes (8)	Yes	Yes	Yes (none)	Partial	Lateral ventricles (b/l)	No
15.	M	10	IS	No	TSC2	Yes (10)	Yes	Yes	Yes (none)	Partial	Foramen of Monro (L)	No
16.	M	2	IS	No	TSC2	Yes (8)	Yes	Yes	Yes (left frontal lobe)	Partial	Lateral ventricles (b/l)	No
17.	F	12	Fits	No	TSC2	Yes (8)	Yes	Yes	Yes (none)	No	Foramen of Monro (b/l)	Yes
18.	M	4	Fits	No	TSC2	Yes (8)	Yes	Yes	Yes (none)	No	Foramen of Monro (b/l)	Yes
19.	F	9	DD, RM, IS	No	TSC2	Yes (11)	Yes	Yes	Yes (left temporal lobe)	Partial	Lateral ventricles (b/l)	No
20.	F	1	HS, RM, IS	No	TSC2	No	No	No	Yes (none)	Partial	Lateral ventricles (b/l)	No
21.	F	2	IS, RM	No	TSC2	Yes (8)	Yes	Yes	Yes (none)	No	Foramen of Monro (L)	Yes
22.	M	72	Fits	No	TSC2	Yes (9)	No	No	Yes (left temporal lobe)	Partial	Foramen of Monro (L)	Yes
23.	F	2	IS	No	TSC2	Yes (8)	Yes	Yes	Yes (none)	No	Foramen of Monro (b/l)	No
24.	F	24	Fits	No	TSC2	Yes (6)	Yes	Yes	Yes (left frontal lobe)	Partial	Frontal horn (L)	No
25.	M	1	RM, LD	Yes	TSC2	No	Yes	Yes	Yes (all left sided lobes)	Partial	Lateral ventricles (b/l)	No
26.	F	2	IS, DD	No	TSC2	Yes (9)	Yes	Yes	Yes (none)	No	Frontal horn (R)	Yes
27.	M	4	Fits	No	TSC2	No	Yes	Yes	Yes (none)	Partial	Foramen of Monro (R)	Yes
28.	F	11	Fits	Yes	TSC2	Yes (6)	Yes	Yes	Yes (none)	No	Lateral ventricles(B/l)	No
29.	F	2	RM, HS	No	TSC2	Yes (9)	No	No	Yes (none)	No	None	No
30.	F	9	Fits	No	TSC2	Yes (7)	No	No	Yes (none)	No	Frontal horn (R)	Yes
31.	M	3	Fits	No	TSC2	Yes (8)	No	No	Yes (none)		Lateral ventricles (b/l)	No
32.	F	12	Fits, LD	Yes	None	Yes (9)	No	Yes	Yes (left parietal lobe)	Partial	Lateral ventricles (b/l)	No
33.	M	36	Fits	Yes	None	No	No	No	Yes (none)	No	Foramen of Monro (b/l)	No
34.	M	0	HS	No	TSC2	No	No	No	Yes (none)	Partial	Foramen of Monro (b/l)	Yes
35.	M	36	DD	No	None	No	No	Yes	Yes (right frontal lobe)	Partial	Foramen of Monro (b/l)	No
36.	F	9	Fits	No	TSC 1	Yes (5)	No	No	Yes (both frontal lobes)	No	None	No
37.	F	2	RM, IS	No	TSC2	Yes (8)	No	No	Yes (left frontal lobe)	No	Lateral ventricles (b/l)	No
38.	F	8	Fits	No	None	Yes (8)	Yes	Yes	Yes (left frontal and right occipital lobes)	Partial	Foramen of Monro (R)	No

DD: developmental delay, LD: learning disabilities, E-CHESS: early childhood epilepsy severity score, SEN: subependymal nodules, SEGA: subependymal giant cell astrocytoma, b/l: bilateral, M: male, F: female, RM: rhabdomyoma, IS: infantile spasm, HS: hypopigmented spots, FM: Foramen of Monro, LV: lateral ventricle, FH: frontal horn, L: left, R: right

Table 3 - Frequency of tuberous sclerosis associated neuropsychiatric disorders features among tuberous sclerosis patients (n=29).

TAND features	Present	Absent	Percentages (%)
Temper tantrum	5	24	17.24%
Aggressive outbursts	8	21	27.59%
Anxiety	1	28	3.45%
Depressed mood	8	21	27.59%
Self-injury	1	28	3.45%
Difficulties paying attention	18	11	62.07%
Overactivity/hyperactivity	11	18	37.93%
Impulsivity	8	21	27.59%
Absent or delayed onset of language to communicate	21	8	72.41%
Poor eye contact	13	16	44.83%
Repetitive behaviours	3	26	10.34%
Sleep difficulties	4	25	13.79%
Difficulties with eating	5	24	17.24%
Extreme shyness	1	28	3.45%
Mood swings	11	18	37.93%
Repeating words or phrases over and over again	2	27	6.90%
Difficulties getting on with peers	11	18	37.93%
Very rigid or inflexible about how to do things	7	22	24.14%
Restlessness or fidgetiness	1	28	3.45%
ASD	12	16	42.86%
ADHD	7	22	24.14%
Intellectual disability	20	9	68.97%
Reading	19	10	65.52%
Writing	20	9	68.97%
Spelling	20	9	68.97%
Mathematics	19	10	65.52%
Multitasking	12	17	41.38%
Memory	15	14	51.72%
Visuo-spatial tasks	11	18	37.93%
Cognitive flexibility	10	19	34.48%
Low self-esteem of the patient	1	28	3.45%
Family stress	9	20	31.03%
Relational difficulties of the patient	6	23	20.69%

Values are presented as numbers and percentages (%).
TAND: tuberous sclerosis complex associated neuropsychiatric disorders,
ASD: autistic spectrum disorder, ADHD: attention deficit hyperactivity disorder

frequency of ISs.[24-26] We found E-CHESS to be a reliable tool for monitoring the severity of epilepsy, evaluating treatment adequacy, and predicting the degree of intellectual impairment, as was originally intended by Humphrey et al.[15] The epilepsy severity and effective seizure control determine the neurocognitive outcome in TSC patients. This was confirmed by our cohort having a high frequency of TAND at behavioral, intellectual, academic, and psychiatric levels. In a study carried out in Italy based on a sample size similar to ours, Toldo et al[27] found that 84% of their patients had at least one TAND and 78% had 4 TAND features. In agreement with our findings, TAND features were found in all domains with some variations that could be explained by cultural norms or inter-observer variation. De Vries et al[28] reported a 21% incidence of ASD and 19% incidence of ADHD in TSC patients within the context of tuberous sclerosis registry to increase disease awareness. This multi-center and international disease registry has been designed to provide deeper insights into the TSC manifestations and management.[28] While higher ASD and ADHD frequencies (ranging between 30-60%) have been reported by other researchers, our findings were in line with those obtained in the above

Table 4 - Severity of epilepsy and response to therapy using the "early childhood epilepsy severity score" (N=30).

Seizure characteristics	n (%)
*Frequency**	
No seizures	10 (33.3)
Weekly	14 (46.6)
Daily	6 (20.0)
More than daily	0 (0.0)
Time period	
Less than one month	8 (26.6)
1-6 months	6 (20.0)
More than 6 months	16 (53.3)
*No of seizure types**	
1	25 (83.3)
2	4 (13.3)
3	1 (3.3)
Anticonvulsants	
None	3 (10.0)
1-2	15 (50.0)
3	12 (40.0)
Response to treatment	
Complete cessation	19 (63.3)
Partial cessation	8 (26.6)
No response	3 (10.0)
E-CHESS score	
2-7	9 (30.0)
More than 7	21 (70.0)

Values are presented as numbers and percentages (%).
*Seizure types: infantile spasms: 14, tonic/clonic:12, absence: 5, atonic: 3, tonic: 3, focal: 3, myoclonic:2, behaviour arrest: 2, and no epilepsy: 8.
E-CHESS: early childhood epilepsy severity score

studies. Interestingly, none of our patients were reported to have anxiety or depressive disorders, possibly due to the younger age of our cohort and parental reluctance to report mental health problems.

Tubers, RMLs, and SENs are present in the majority of TSC patients. The number and location of tubers correlate to the severity of epilepsy and the degree of cognitive deficit. Although RMLs have no prognostic implications with respect to TSC severity, tubers are believed to be responsible for symptomatic epilepsy in approximately 75% of patients.[31] The frequency with which tubers, SENs, and SEGAs were observed in our cohort was similar to that reported previously.[32] The frequency with which tubers, SENs, and SEGAs were observed in our cohort was similar to that reported previously.[31,33,34] A total of 5 (62.5%) of the patients with SEGA in our cohort received everolimus, and only 2 (25%) of these required surgical management. It is reasonable to assume that more patients would have required neurosurgical intervention in the absence of mTOR inhibitor treatment. However, as our sample size was small, a longitudinal study with a larger sample would be required to reach a definitive conclusion.

Study strengths & limitations. Our results will provide a baseline for future research into TSC manifestations and management. In common with all retrospective studies, we were limited by the quality of data recorded in the electronic medical records. Some of the subjective manifestations, especially TAND, are likely to have been under-reported, due to social stigma. Details of the presentation are subject to recall bias.

In conclusion, we have reported the clinical and radiological features of TSC in pediatric patients seen at Sidra Medicine and Hamad General Hospital, Doha, Qatar. While the incidence and phenotype of the disease were similar to those seen in other populations, a genotypically more severe form of the disease was seen more frequently in our cohort. Diagnostic work-up, management, and surveillance for radiological features were carried out according to the internationally accepted guidelines. We have demonstrated that everolimus has an established role in the treatment of SEGA and as a disease modifying agent for several other TSC manifestations.

As the national referral center for children with TSC, a multidisciplinary management approach (described earlier) has evolved at Sidra Medicine, Doha, Qatar. This can be further improved in the future by expanding the core team, and extending the management to age specific specialist teams.

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