Manifestations of Tuberous Sclerosis Complex: The Experience of a Provincial Clinic

Colin Wilbur, Chinnuwat Sanguansermsri, Hedi Chable, Mihaela Anghelina, Sharon Peinhof, Kelly Anderson, Paul Steinbok, Ash Singhal, Anita Datta, Mary B. Connolly

ABSTRACT: *Background:* Tuberous sclerosis complex (TSC) is a neurocutaneous disorder with a wide spectrum of manifestations. Recent consensus recommendations stress the importance of multidisciplinary management of children with TSC. The objective of this study was to examine the manifestations of TSC at a large referral centre to determine the care needs of this population. *Methods:* A retrospective, systematic chart review was performed of children with TSC managed at British Columbia Children's Hospital. Patients were identified through epilepsy and clinical neurophysiology databases. *Results:* The study population comprised 81 patients, born between 1987 and 2014, who were a median of 10 years (range, 0.2-23.2) at most recent follow-up. Epilepsy occurred in 91% of patients, including 32% with a history of infantile spasms. Nineteen patients underwent epilepsy surgery, nine (47%) of whom were seizure-free at most recent follow-up. Overall, 61% of epilepsy patients had been seizure-free for at least 1 year at the time of last follow-up. Neuropsychiatric disorders were diagnosed in 49% of children, with autism (25%), attention deficit hyperactivity order (19%) and anxiety (16%) being the most common. Cardiac rhabdomyomata occurred in 35% of children and renal angiomyolipomas were seen in 43%. A total of 91% had skin manifestations. *Conclusions:* This study outlines the multisystem manifestations of TSC, observed through a large pediatric referral center. Epilepsy and neuropsychiatric disorders are the major source of morbidity in this age group and provide many challenges to the treating clinician. Because a subset of the study population is still quite young, the prevalence of neuropsychiatric disorders is likely underestimated.

RÉSUMÉ: Manifestations du complexe de la sclérose tubéreuse : l'expérience d'une clinique provinciale. *Contexte:* La sclérose tubéreuse (ST) est une maladie neurocutanée comportant un large éventail de manifestations. Des recommandations consensuelles récentes ont souligné l'importance de la prise en charge multidisciplinaire des enfants atteints de ST. Le but de cette étude était d'examiner les manifestations de la ST chez les patients fréquentant un important centre de référence afin de déterminer quels sont les soins dont cette population a besoin. *Méthodologie:* Nous avons effectué une revue rétrospective systématique des dossiers d'enfants atteints de ST traités au Children's Hospital de la Colombie Britannique. Les patients ont été identifiés dans les bases de données contenant des renseignements sur l'épilepsie et la neurophysiologie. *Résultats:* Quatre-vingt-un patients nés entre 1987 et 2014, dont l'âge médian était de 10 ans (écart de 0,2 à 23,2) au moment de la plus récente visite de suivi, ont été identifiés. Quatre-vingt-onze pour cent des patients présentaient de l'épilepsie, dont 32% avaient une histoire de spasmes infantiles. Dix-neuf patients ont subi une chirurgie pour épilepsie, dont 9 (47%) n'ont pas présenté de crises après la chirurgie, selon l'information consignée au dossier à la plus récente visite de suivi et 61% des patients épileptiques n'avaient pas présenté de crise au cours de la dernière année. Des troubles neuropsychiatriques ont été diagnostiqués chez 49% des enfants, dont les plus fréquents étaient l'autisme (25%), le trouble du déficit de l'attention avec ou sans hyperactivité (19%) et un trouble anxieux (16%). Trente-cinq pour cent des enfants étaient porteurs de rabdomyomes cardiaques et 43% d'angiomyolipomes rénaux. Dans l'ensemble, 91% présentaient des manifestations cutanées. *Conclusions:* Cette étude décrit les manifestations multisystémiques de la ST observées dans un grand centre pédiatrique de référence. L'épilepsie et les troubles neuropsychiatriques sont la source majeure de morbidité dans ce groupe d'âge et de défis importants pour le médecin traitant. La prévalence des troubles neuropsychiatriques est vraisemblablement sous-estimée parce qu'une partie de la population étudiée est encore jeune.

From the Division of Neurology, Department of Pediatrics, British Columbia Children's Hospital and University of British Columbia (CW, CS, HC, MA, SP, KA, AD, MBC); Division of Neurosurgery, Department of Surgery, British Columbia Children's Hospital and University of British Columbia (PS, AS).
Correspondence to: Dr. Mary B. Connolly, Division of Neurology, Department of Pediatrics, BC Children's Hospital, 4480 Oak Street, Vancouver BC, Canada V6H 3V4; Email: mconnolly@cw.bc.ca.

Tuberous sclerosis complex (TSC) is an autosomal dominant neurocutaneous disorder with an estimated incidence of 1:6000 live births.[1] Two causative genes have been identified. *TSC1* is located on chromosome 9q34 and encodes the protein hamartin,[2] whereas *TSC2* is found on chromosome 16p13 and encodes tuberin.[3] Hamartin and tuberin form a complex that controls cell growth and proliferation through mechanisms that include inhibition of the mammalian target of rapamycin (mTOR) pathway.[4] Understanding the pathophysiology of TSC has led to the development of medications directed at inhibiting the mTOR pathway that have been approved to treat various manifestations of TSC.[5-7]

Clinically, TSC is characterized by hamartomatous growths that can occur in virtually any organ, including the skin, brain, heart, and kidneys and rarely the liver.[8] Diagnostic criteria for TSC have recently been updated and outline 11 major and six minor features that allow for a clinical diagnosis of either definite or possible TSC.[9] Central nervous system manifestations include cortical tubers, subependymal nodules, and subependymal giant cell astrocytomas (SEGAs). Epilepsy is the most common neurologic symptom in childhood, reported in 80% to 90% of patients, and is often resistant to medical therapy.[10] Onset of epilepsy is typically within the first 2 years of life, and more than one-third of patients may develop infantile spasms.[11] Tuberous sclerosis-associated neuropsychiatric disorders occur in most individuals with TSC, are often underdiagnosed, and cause significant morbidity.[12] Autism spectrum disorder is the most common psychiatric diagnosis, reported in 17% to 61% of patients,[13] whereas approximately half of patients have intellectual disability, often in association with autism.[14]

Recommendations have recently been developed that outline a framework to optimize and standardize the surveillance and care for patients with TSC.[15] These underscore the importance of a multidisciplinary team familiar with the management of TSC. The objective of this study was to assess the manifestations of TSC as seen through the neurology department at a large Canadian provincial children's hospital. We hope that this will assist in identifying the resources to provide in a multidisciplinary TSC clinic and to optimize ongoing patient care.

METHODS

This retrospective study was approved by the University of British Columbia Clinical Research Ethics Board. All patients were assessed through the Pediatric Neurology clinic at British Columbia Children's Hospital between 1990 and 2014. Patients were identified through prospectively maintained epilepsy and clinical neurophysiology databases as well as referrals to the TSC clinic, which was established in 2012. Data were obtained by systematic chart review.

Patients were included if they met the diagnostic criteria for definite TSC, as outlined by the 2012 International Tuberous Sclerosis Consensus Conference.[9] Epilepsy was diagnosed by a documented history of two or more unprovoked seizures. Seizure types were classified according to the International League Against Epilepsy Commission on Classification and Terminology.[16] Patients were considered seizure-free if there was a minimum of 1 year following the last documented seizure at the time of most recent follow-up. Developmental delay and psychiatric conditions were reported as present when those diagnoses were documented by a pediatrician, psychiatrist, or neurologist.
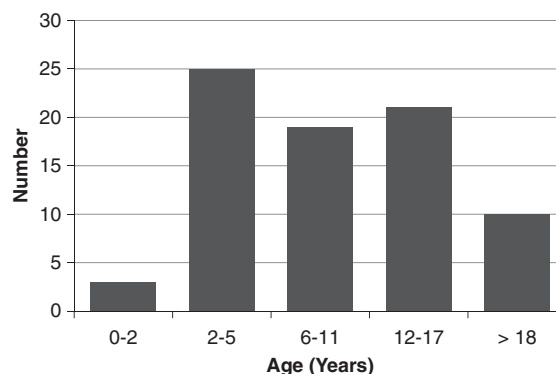

Figure 1: Number of Patients by Age at most recent follow-up.

The end point of follow-up was considered as the time of the last documented clinical neurology visit.

Clinical data were analyzed descriptively. The proportions of patients manifesting various clinical features are reported and, where applicable, median values are reported along with the range of values obtained. Because of the population size and retrospective nature, the aim of this study was primarily descriptive, and so comparative statistical analysis was not performed.

RESULTS

Study Population

A total of 81 patients were identified who were born between 1987 and 2014. Genetic testing for TSC is not routinely funded in the province of British Columbia, but six patients (7%) had genetic confirmation of diagnosis (two *TSC1*, four *TSC2*). Forty-one (51%) were male. The median age at most recent clinical follow-up was 10.0 years (range, 0.2-23.2) (Figure 1). Eleven children (14%) were diagnosed with TSC antenatally, based on the presence of cardiac rhabdomyomata on prenatal ultrasound. Six patients (7%) had a documented family history of TSC in a first-degree relative.

Epilepsy

Seventy-four patients (91%) had a diagnosis of epilepsy. The median age at seizure onset was 12 months (range, 0-168) (Table 1). The initial seizure type was most commonly focal (66%), followed by epileptic spasms (26%) and generalized (5%). Fifteen patients (20%) had a documented history of status epilepticus, occurring at a median age of 15 months (range, 2-180). At the most recent follow-up, 45 (61%) were seizure-free for a median 4.5 years (range, 1-15), including eight (11%) who were seizure-free off antiseizure medications. Patients were on a median of one antiseizure medication (range, 0-5) and had failed a median of two medications (range, 0-10).

Overall, 32% of patients developed infantile spasms at a median age of 5 months (range, 0.25-30). Vigabatrin successfully treated spasms in 18 of 21 patients (86%) in whom it was tried, whereas corticosteroids were successful in one of three patients (33%).

Those younger than age 12 months at first seizure most often had epileptic spasms as their initial seizure type (54%), whereas those 12 months of age and older at seizure onset most often had focal seizures as their initial seizure type (84%) (Figure 2). A total of 71%

Table 1: Epilepsy Details

Number of patients with epilepsy	74
Median age of seizure onset (range)	12 months (0-168)
Initial seizure type	
Focal	49 (66%)
Generalized	4 (5%)
Epileptic spasms	19 (26%)
Unknown	2 (3%)
Infantile spasms	24 (32%)
Infantile spasms treatment	
Vigabatrin successful	18/21
Steroids successful	1/3
Status epilepticus	15 (20%)
Seizure-free at last follow-up	45 (61%)
Median duration seizure-free (range)	4.5 years (1-15)

Table 2: Epilepsy Surgery Population

Epilepsy surgery	19
Median age of seizure onset (range)	5 (0-22) months
Median age first surgery (range)	4.8 (1.1-15.6) years
Infantile spasms	8 (42%)
First surgery type	
Frontal resection	12
Parietal resection	2
Temporal resection	1
Multilobar resection	2
Total corpus callosotomy	2
Second surgery	4 (21%)
Frontal resection	2
Multilobar resection	1
Total corpus callosotomy	1
Seizure-free	9 (47%)
Median duration seizure-free (range)	2.5 (1-9) years

of children who had seizure onset after 12 months of age were seizure-free at most recent follow-up, compared with 49% seizure-free in those who had seizure onset before 12 months of age.

Epilepsy Surgery

Nineteen patients (26% of those with epilepsy) underwent epilepsy surgery on at least one occasion (Table 2). Surgery was performed following video-electroencephalogram (EEG) monitoring, high-resolution magnetic resonance imaging (MRI) and neuropsychological testing. In some cases, functional imaging using subtraction ictal SPECT coregistered with MRI. Rarely, positron emission tomography using alpha-methyl-tryptophan was performed. In those who underwent surgery, the median age at seizure onset was 5 months (range, 0-22). Their initial seizure type was focal in 12 (63%), epileptic spasms in six (32%), and generalized in one (5%). Twelve (63%) eventually developed multiple seizure types and all had focal seizures. These patients had failed a median of four antiseizure medications (range, 2-10).
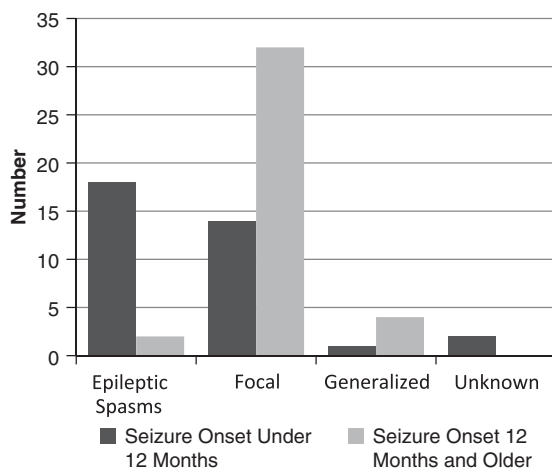

Figure 2: Seizure type and age at onset.

The median age at first surgery was 4.8 years (range, 1.1-15.6), whereas the last follow-up occurred a median 2.4 years (range, 0.2-16.2) following the initial surgery.

The initial surgery in 17 children was tuberectomy with resection of epileptogenic cortex guided by electrocorticography, whereas total corpus callosotomy was performed in two children. Surgery was most commonly in the frontal lobe (12 patients). Surgical complications were reported in four patients (21%), all of whom had a postoperative hemiparesis. This resolved completely in two patients, whereas two children had persistent mild hemiparesis that improved with time, but did not recover fully. The motor deficits were predicted based on the resected tuber involving or being adjacent to the motor cortex. One patient also developed chemical meningitis on postoperative day 3, which resolved completely with steroids.

Four patients (21%) underwent a second epilepsy surgery because of ongoing seizures, at a median of 23 months (range, 7-32) following the first surgery. One patient initially underwent a complete corpus callosotomy for disabling drop attacks, after which his seizures became focal in nature and he became seizure-free following a subsequent right frontal resection. A second patient had extension of a previous right frontal resection, which resulted in a seizure-free outcome. A third patient underwent a multilobar resection following a previous frontal resection, but did not have a reduction in seizure frequency. Finally, the fourth patient developed drop attacks following initial frontal tuber and cortical resection, and then underwent a total corpus callosotomy. This patient experienced a 50% to 90% reduction in seizure frequency.

Figure 3 illustrates seizure outcome following surgery based on the most recent follow-up. Nine patients (47%) were seizure-free, with a median seizure-free duration of 2.5 years (range, 1-9). Only two patients (11%) had less than a 50% reduction in seizure frequency following epilepsy surgery. At most recent follow-up, these patients were on a median of two antiseizure medications (range, 0-5), including one patient who was seizure-free off medication.
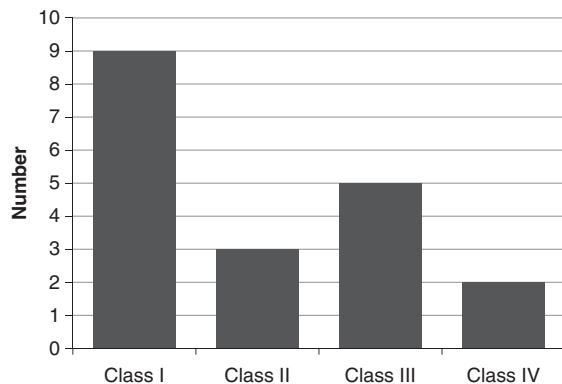
Figure 3: Seizures outcome following epilepsy surgery (Engel Classification).

In patients who underwent resective surgery, compared with those with ongoing seizures, patients who were seizure-free tended to have an older age at seizure onset, less frequent history of infantile spasms, and a lower rate of autism (Table 3).

Structural Central Nervous System Abnormalities

All patients had neuroimaging available for review: 78 had at least one brain MRI and 3 had at least one head computed tomography, but no MRI. Cortical tubers were identified in 80 patients (99%). Seventy-nine patients (98%) had subependymal nodules on neuroimaging. Fifteen patients (19%) had evidence of a SEGA on neuroimaging, first identified at a median age of 9.5 years (range, 1-17.5) (Figure 4A). Of these, four underwent surgical resection of the SEGA.

Other imaging findings included a pituitary prolactinoma that was identified in one patient who developed secondary central hypothyroidism. Another patient developed a suprasellar arachnoid cyst with secondary growth hormone deficiency (Figure 4B), requiring endoscopic cyst fenestration. A third developed a meningioma, which was surgically resected. One patient had a cerebellar tuber.

Cardiac

Cardiac rhabdomyomata were documented in 28 patients (35%) (Table 4). However, only three patients (11%) had clinical symptoms, which were all related to arrhythmia. This included one patient who developed supraventricular tachycardia and secondary congestive heart failure at the age of 17 months that was treated with

Table 3: Comparison of seizure-free patients and those with ongoing seizures following surgery

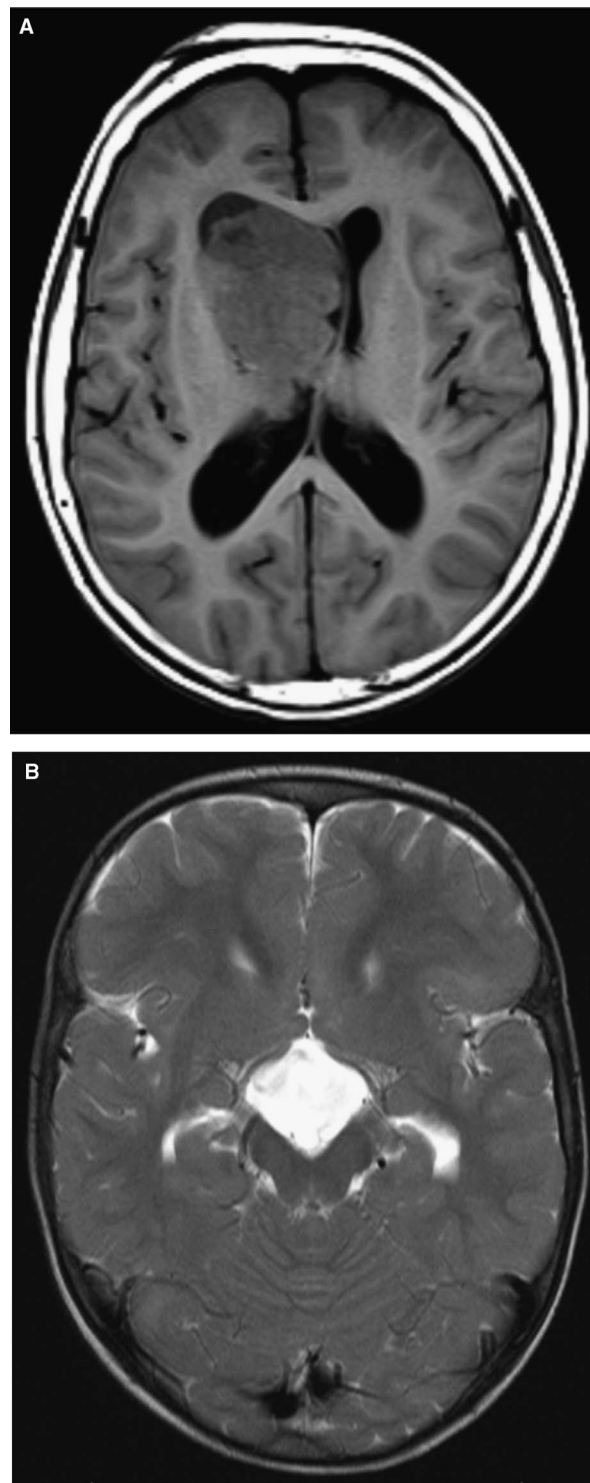|	Seizure-free	Ongoing seizures
Number	9	9
Median age of seizure onset (range)	15 months (0.5-22)	5 months (0-13)
Seizure onset before age 1 year	4 (44%)	8 (89%)
Median age at surgery (range)	93 months (13-174)	36 months (31-117)
History of infantile spasms	1 (11%)	6 (67%)
Intellectual disability	5 (56%)	4 (44%)
Autism	3 (33%)	6 (67%)

Figure 4: (A) Large right intraventricular SEGA (T1 weighted axial image); (B) Suprasellar cyst (T2 weighted axial image).

amiodarone, which was later discontinued. A second patient developed fetal supraventricular tachycardia at 30 weeks' gestation, requiring treatment with flecainide, which was discontinued at age 1 year. A third patient had inducible ventricular tachycardia, requiring an implantable defibrillator. No other patients required

Table 4: Systemic manifestations of TSC

Cardiac rhabdomyomas	28 (35%)
Renal angiomyolipomas	35 (43%)
Multiple renal cysts	10 (12%)
Polycystic kidneys	3 (4%)
Dermatologic manifestations	74 (91%)
Hypopigmented macules	62 (77%)
Facial angiofibroma	35 (43%)
Shagreen patch	20 (25%)
Forehead plaque	19 (12%)
Cafe-au-lait macules	8 (10%)
Collagenomas	4 (5%)
Peri-/subungual fibromas	3 (4%)
Confetti lesions	2 (2%)
White hair locks	2 (2%)
Ophthalmologic manifestations	21 (26%)
Retinal hamartomas	13 (16%)
Retinal achromatic patch	4 (5%)
Psychiatric manifestations	40 (49%)
Autism spectrum disorder	20 (25%)
Attention deficit hyperactivity disorder	15 (19%)
Anxiety	13 (16%)
Obsessive-compulsive behaviours	5 (6%)
Depression	3 (4%)
Intellectual disability by standardized testing	27 (33%)
Mild	10
Moderate	11
Severe	6
Developmental delay	53 (65%)

cardiac surgery and no cardiac abnormalities were reported in patients without a history of rhabdomyomata.

Renal

Thirty-five patients (43%) had at least one renal angiomyolipoma (AML) noted on ultrasound, including 15 with multiple AMLs. One patient with multiple AMLs underwent a partial nephrectomy because of concern of a renal cell carcinoma raised on renal MRI. Pathology of the excised lesion demonstrated a fat-poor AML. No other patients have undergone any treatment for their AMLs to date and no renal malignancies were identified in this population. An additional 15 patients (19%) had multiple renal cysts on ultrasound, whereas two children (2%) had polycystic kidney disease. Only one patient had impaired renal function, with renal ultrasound demonstrating a single AML and multiple renal cysts, but has not required treatment. An additional patient with multiple AMLs and renal cysts developed hypertension, requiring treatment with an ACE inhibitor, with no other cause for the hypertension found.

Dermatologic

A total of 74 patients (91%) had at least one dermatologic manifestation of TSC. The most common findings were hypo-pigmented macules in 62 (77%), facial angiofibromas in 35 (43%), and Shagreen patch in 20 (25%). Only one patient younger than 6 years old was noted to have facial angiofibromas. Treatment was documented in nine patients with facial angiofibromas and included laser therapy, cryotherapy, and use of a topical mTOR inhibitor. The frequency of less common skin findings is outlined in Figure 8.

Ophthalmologic

Twenty-one patients (26%) had at least one eye finding. Retinal hamartomata were seen in 13 patients (16%). This included one patient with markedly decreased vision, to the level of counting fingers, related to a hamartoma involving the optic nerve. Retinal achromatic patch was seen in 5%, whereas strabismus was noted in 4%. One patient had a unilateral Horner's syndrome without an identifiable cause.

Psychiatric

Forty patients (49%) had at least one documented psychiatric diagnosis or behavioral abnormality. The most common diagnosis was autism spectrum disorder, reported in 20 patients (25%), all of whom had epilepsy. This was followed by attention deficit hyperactivity order (ADHD) in 15 (19%) and anxiety in 13 (16%). Common behavioral concerns included sleep difficulty (12%), aggression (11%), and impulsivity (9%). Thirty-two patients (40%) were assessed as having intellectual disability, either on standardized testing (27) or clinically (5). For individuals with intellectual disability diagnosed on formal testing, it was classified as mild in 10, moderate in 11, and severe in six. Fifty-three patients (65%) had a history of developmental delay. When classified by age of seizure-onset, rates of intellectual disability were similar in those with seizure onset before 12 months (43%) compared with after 12 months (37%).

When only those 52 patients who were school-aged (6 years and older) at last follow-up are considered, 32 (62%) had at least one psychiatric diagnosis. Autism was present in 17 school-aged children (33%), all except one of whom had intellectual disability. ADHD was present in 15 (29%) and anxiety in 11 (21%). Twenty-nine (56%) had intellectual disability, 27 based on standardized testing. Of all school-aged patients, 12 (23%) were functioning at grade level, seven (13%) were below grade level, 18 (35%) were in a modified or life skills program, and the school level was unknown in the remainder.

All patients diagnosed with autism spectrum disorder had a history of epilepsy. Patients with autism tended to have an earlier age of seizure onset, a higher rate of infantile spasms, more treatment-resistant epilepsy, and had higher rates of intellectual disability (Table 5).

Miscellaneous

One patient developed a lumbar hamartoma requiring surgical resection. Pathological examination demonstrated a benign nodular fibrous hamartoma. One patient was born with bilateral cleft lip and palate and hemivertebrae at T1 and T5, whereas another had congenital lymphedema of the left arm.

DISCUSSION

This study outlines the spectrum of TSC manifestations observed at a provincial pediatric neurology referral centre.

Table 5: Comparison of patients with and without Autism Spectrum Disorder

	Patients with autism (N = 20)	Patients without autism (N = 61)
Male	8 (40%)	33 (54%)
Epilepsy	20 (100%)	54 (89%)
Median age of seizure onset (range)	8 (0-36) months	12 (0-168) months
Infantile spasms	9 (45%)	15 (25%)
Proportion with epilepsy seizure-free	9 (45%)	36 (67%)
Median number of failed antiseizure medications (range)	4 (1-10)	2 (0-8)
Median number of current antiseizure medications (range)	2 (1-4)	1 (0-3)
Intellectual disability	18 (90%)	14 (23%)

Epilepsy was the most common symptom presenting in childhood, occurring in 91% of our patients, with most patients having seizure onset in the first 2 years of life. This is similar to the rate of 75% to 93% reported in other studies.[11,17,18] Although epilepsy was typically treatment resistant in these patients, with most failing multiple antiseizure medications, 61% were at least 1 year seizure-free at the time of their last follow-up. This is better than recent reports in the literature, where only 32% to 49% achieved a period of 1-year seizure-freedom.[19,20] The correlation between later age of seizure onset and improved seizure outcome has previously been reported in these studies. Approximately one-third of TSC patients have been reported to develop infantile spasms, most often in the first year of life,[21,22] which is similar to our experience. We found that 86% of TSC patients with infantile spasms who were treated with vigabatrin had cessation of their spasms, comparable to the response rate of up to 95% previously reported.[23] Given the ascertainment of patients through a neurology clinic, our study may overestimate the frequency and severity of epilepsy in the overall population with tuberous sclerosis complex.

The role of surgical treatment for treatment-resistant focal epilepsy is increasing, with evidence that outcomes following surgery are superior to medical therapy.[24] TSC is different from most focal epilepsies in that there is an underlying genetic abnormality and there are often multiple potentially epileptogenic lesions located outside of the area of resection. Despite this, outcomes from epilepsy surgery in TSC are generally positive, with up to 55% to 60% of patients reported to become seizure-free and only 10% having a reduction in seizures of less than 50%.[25-27] Outcomes in our study population were very similar, with 47% being seizure-free and 10% having less than a 50% improvement following surgery.

The results of studies looking at outcome predictors for seizure-freedom following epilepsy surgery in TSC have been inconsistent. Clinical variables reported to be associated with a good postoperative outcome include the absence of tonic or generalized seizures, a milder degree of intellectual impairment, seizure onset after the first year of life, preoperative hemiparesis, unifocal EEG abnormalities, and concordance between EEG and neuroimaging studies.[25,27-29] Our study was not designed to examine predictors of outcome following surgery, although those with recurrent seizures after surgery tended to be younger at seizure onset and had a higher rate of infantile spasms. Some of the surgical patients in our cohort were analyzed as part of a recent multicenter, international, retrospective cohort study, which found that larger surgical resections (greater than a tuberectomy) were associated with a longer duration of seizure freedom postoperatively.[30] The surgical complication rate in our cohort was low, similar to that reported in other studies,[31] with transient or mild hemiparesis being the most common complication. This was a predictable risk associated with frontal resection of tubers in close proximity to the motor area. Thus, our experience demonstrates that epilepsy surgery is a safe and effective treatment option in carefully selected children with TSC and treatment-resistant epilepsy. Further work is needed to determine the best methods by which to select patients for surgery and whether surgery may improve neurodevelopmental outcomes.[32,33]

The high rate of cortical tubers and subependymal nodules found in our population is similar to that previously described.[34] The ascertainment of patients through a neurology center is likely biased towards a higher rate of central nervous system findings compared to the general TSC population. 15% of our patients developed SEGAs, including two patients who presented symptomatically with dramatic growth in their SEGAs. Under the current guidelines, which recommend surveillance neuroimaging every 1 to 3 years,[15] these patients may have had their growing SEGAs discovered sooner and been candidates for intervention at an earlier point, with potentially less complicated courses. Other rare neuroimaging findings included meningioma, pituitary adenoma, and arachnoid cyst. There have been rare reports of these associated with TSC in the literature,[35-37] which may represent incidental associations or a common pathogenic mechanism.

The systemic manifestations of TSC in our population are similar to those reported in the literature. We found a rate of cardiac rhabdomyomata of 35%, compared with the 30% to 50% reported rate.[34,38] Only three of our patients became symptomatic from their rhabdomyomata, all related to arrhythmias, including one with congestive heart failure secondary to arrhythmia. Arrhythmia is the most common cardiac complication, reported in up to 25% of patients with rhabdomyomata,[39] whereas only 2% to 5% of patients develop significant hemodynamic compromise and heart failure. The natural history of cardiac rhabdomyomata is spontaneous regression, so most patients will have improvement in their cardiac status over time without surgical intervention. Similarly, the 43% rate of angiomyolipomas in this study is comparable to the 40% to 80% previously reported.[34,40] The rate of renal cysts in our study, 19%, is at the low end of the 17% to

47% rate reported in these studies. Although typically asymptomatic in childhood, these lesions tend to increase in size over time and can lead to hypertension, hemorrhage, and end-stage renal disease.[41] Thus, the low rate of renal dysfunction and need for intervention in our population would be expected to change as patients age. Retinal hamartomas are the most common ophthalmic manifestation of TSC, reported in 44% of a population-based study.[42] The low rate in our population, 16%, is likely an underestimate related to the retrospective nature of the study. We describe one patient born with bilateral cleft lip and palate, which has only rarely been described in association with TSC.[43] One patient in our study was born with congenital focal lymphedema, which is an uncommon association with TSC and may reflect a shared pathophysiology.[44]

Psychiatric and behavioral comorbidities were very common, affecting half of patients in our study. Autism was the most common problem, diagnosed in 20%. The reported rates of autism in TSC range from 17% to 61%.[13] Patients with autism in our study tended to have a younger age at seizure onset, a higher rate of infantile spasms, and more treatment resistant epilepsy—factors that have previously been suggested as risk factors for developing autism in the TSC population.[45,46] The majority of patients with autism had comorbid intellectual disability, with the overall prevalence of intellectual disability in our study population being 40% and most often in the moderate-severe range. Previous studies have reported a rate of intellectual disability around 50% in TSC patients, with a significant portion falling in the profound range.[14] ADHD was the most prevalent diagnosis after intellectual disability and autism, occurring in 29% of our school-aged patients, while other studies have reported a rate of approximately 30% to 60%.[47] The slightly lower rate of autism and other neuropsychiatric diagnoses compared with the literature may reflect, in part, the absence of standardized screening or reporting of neuropsychiatric manifestations when these children were assessed. Therefore, these comorbidities may have been missed or not accurately captured in the retrospective review. Early screening for autism spectrum disorders in children with TSC should be recommended, and some research groups are looking for early biomarkers of autism in this population. Additionally, a portion of the cohort was at a young age at last follow-up and many neuropsychiatric problems may not become evident until children are older. Indeed, if only children of school age in this cohort are considered, one-third had a diagnosis of autism and 56% had intellectual disability.

This study is limited by its retrospective nature because there was no standardized protocol for investigation, surveillance, or management in the study population. As a result, the reported rates of TSC manifestations may be an underestimation. Furthermore, recruitment through neurology department records may have missed a proportion of children with TSC without neurologic manifestations. However, this study is likely an accurate reflection of the TSC-associated neurologic manifestations seen at a tertiary referral centre. Overall, this study reinforces the spectrum of TSC manifestations in childhood, placing particular emphasis on the burden of neurologic morbidity. Further prospective studies will be useful in confirming these findings. In particular, formal neuropsychiatric screening will provide useful adjunctive information for future studies in this population. The tuberous sclerosis-associated neuropsychiatric disorders checklist has recently been developed as a guide to assist physicians in identifying neuropsychiatric concerns through discussion with patients and their families.[48]

These results have contributed to the ongoing development of a TSC clinic at British Columbia Children's Hospital. Given the prominence of epilepsy in this population, the clinic is directed by two pediatric epileptologists (MC, AD) who are also involved in the epilepsy surgery program, supported by neurology nurses familiar with TSC. Thus, patients who are potential candidates for epilepsy surgery may be identified early. For those patients who undergo epilepsy surgery, the neurosurgeon may attend the clinic for coordinated follow-up. A medical geneticist also attends the clinic to provide genetic counseling as required. To address the potential underestimation of the rate of neuropsychiatric comorbidities identified in our study population, standardized screening has been instituted. Patients between the age of 18 months and 3 years are screened for autism at each visit using the Modified Checklist for Autism in Toddlers, Revised with Follow-up.[49] Those with a positive screen are then referred to a developmental pediatrician for formal assessment. School-aged children are screened annually for ADHD using the SNAP-IV 26 Rating Scale[50] and additional challenges are sought using the Strengths and Difficulties Questionnaire[51] and the Pediatric Quality of Life Inventory.[52] A neuropsychiatrist with expertise in genetic disorders now participates in the TSC clinic. It is hoped that the identification of patient needs through this prospective screening will further facilitate the direct involvement of neuropsychology and clinical psychology in the TSC clinic. Because manifestations outside the nervous system are common, our patients are routinely assessed and followed as required by other disciplines including cardiology, nephrology, dermatology, and ophthalmology. However, because our results demonstrate that these systemic manifestations are most often asymptomatic, these disciplines do not necessarily need to be involved at every visit. Therefore, we envision the TSC clinic as a combination of a core "physical clinic," focusing on neurologic and neuropsychiatric manifestations, supported by a network of specialists knowledgeable in TSC, but who do not necessarily attend the physical TSC clinic. The development of this clinic is an ongoing process and we plan to regularly reassess its structure and the services it provides though prospective data collection and feedback from our patients, their families, and other health care professionals.

CONCLUSION

TSC is a challenging disease, both for clinicians and for affected patients and their families. As described in this study, they are often faced with treatment resistant epilepsy, complex neuropsychiatric manifestations, and systemic medical complications that evolve with age. In recognition of these issues, we have established a dedicated tuberous sclerosis clinic that continues to evolve in an effort to improve patient care. It is hoped that this clinic will facilitate appropriate monitoring of the disorder and, hopefully, reduce complications for patients. Transition to adult services remains challenging because of the multidisciplinary nature and complexity of this lifelong disease. Increased collaboration between pediatric and adult specialists will help to improve care for patients with TSC across the lifespan.

DISCLOSURES

STATEMENT OF AUTHORSHIP

CW was responsible for developing the data collection database, collecting and analyzing data, and primary manuscript development. CS assisted in analysis of epilepsy data. HC and MA assisted in database development and data collection. SP and KA were involved in primary clinical evaluation of patients. PS and AS were involved in primary clinical evaluation of patients and assisted in analysis of epilepsy surgery data. AD and MC were involved in primary clinical evaluation of patients and assisted in data analysis. MC supervised all aspects of manuscript development. All authors participated in the editing of the final manuscript.

REFERENCES

1. Osborne JP, Fryer A, Webb D. Epidemiology of tuberous sclerosis. Ann N Y Acad Sci. 1991;615:125-7.
2. van Slegtenhorst M, de Hoogt R, Hermans C, et al. Identification of the tuberous sclerosis gene TSC1 on chromosome 9q34. Science. 1997;277:805-8.
3. European Chromosome 16 Tuberous Sclerosis Consortium. Identification and characterization of the tuberous sclerosis gene on chromosome 16. Cell. 1993;75:1305-15.
4. Au KS, Williams AT, Gambello MJ, Northrup H. Molecular genetic basis of tuberous sclerosis complex: from bench to bedside. J Child Neurol. 2004;19:699-709.
5. Franz DN, Belousova E, Sparagana S, et al. Efficacy and safety of everolimus for subependymal giant cell astrocytomas associated with tuberous sclerosis complex (EXIST-1): a multicentre, randomised, placebo-controlled phase 3 trial. Lancet. 2013;381:125-32.
6. Bissler JJ, Kingswood JC, Radzikowska E, et al. Everolimus for angiomyolipoma associated with tuberous sclerosis complex or sporadic lymphangioleiomyomatosis (EXIST-2): a multicentre, randomised, double-blind, placebo-controlled trial. Lancet. 2013;381:817-24.
7. Kotulska K, Chmielewski D, Borkowska J, et al. Long-term effect of everolimus on epilepsy and growth in children under 3 years of age treated for subependymal giant cell astrocytoma associated with tuberous sclerosis complex. Euro J Paediatr Neurol. 2013;17:479-85.
8. Northrup H, Koenig MK, Au KS. Tuberous sclerosis complex. 1999. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews [Internet]. Seattle, WA: University of Washington, Seattle; 1993-2015.
9. Northrup H, Krueger DA, International Tuberous Sclerosis Complex Consensus Group. Tuberous sclerosis complex diagnostic criteria update: recommendations of the 2012 international tuberous sclerosis complex consensus conference. Pediatr Neurol. 2013;49:243-54.
10. Holmes GL, Stafstrom CE, Tuberous Sclerosis Study Group. Tuberous sclerosis complex and epilepsy: recent developments and future challenges. Epilepsia. 2007;48:617-30.
11. Chu-Shore CJ, Major P, Camposano S, Muzykewicz D, Thiele EA. The natural history of epilepsy in tuberous sclerosis complex. Epilepsia. 2010;51:1236-41.
12. Curatolo P, Moavero R, de Vries PJ. Neurological and neuropsychiatric aspects of tuberous sclerosis complex. Lancet Neurol. 2015;14:733-45.
13. Curatolo P, Porfirio MC, Manzi B, Seri S. Autism in tuberous sclerosis. Eur J Paediatr Neurol. 2004;8:327-32.
14. Joinson C, O'Callaghan FJ, Osborne JP, Martyn C, Harris T, Bolton PF. Learning disability and epilepsy in an epidemiological sample of individuals with tuberous sclerosis complex. Psychol Med. 2003;33:335-44.
15. Krueger DA, Northrup H, International Tuberous Sclerosis Complex Consensus Group. Tuberous sclerosis complex surveillance and management: recommendations of the 2012 international tuberous sclerosis complex consensus conference. Pediatr Neurol. 2013;49:255-65.
16. Berg AT, Berkovic SF, Brodie MJ, et al. Revised terminology and concepts of organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005-2009. Epilepsia. 2010;51:676-85.
17. Devlin LA, Shepherd CH, Crawford H, Morrison PJ. Tuberous sclerosis complex: clinical features, diagnosis, and prevalence within Northern Ireland. Dev Med Child Neurol. 2006;48: 495-9.
18. Au KS, Williams AT, Roach ES, 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.
19. Overwater IE, Bindels-de Heus K, Rietman AB, et al. Epilepsy in children with tuberous sclerosis complex: chance of remission and response to epileptic drugs. Epilepsia. 2015;56:1239-45.
20. Vignoli A, La Briola F, Turner K, et al. Epilepsy in TSC: certain etiology does not mean certain prognosis. Epilepsia. 2013;54:2134-42.
21. Saxena A, Sampson JR. Epilepsy in tuberous sclerosis: phenotypes, mechanisms, and treatments. Semin Neurol. 2015;35:269-76.
22. O'Callaghan FJ, Harris T, Joinson C, et al. The relation of infantile spasms, tubers, and intelligence in tuberous sclerosis complex. Arch Dis Child. 2004;89:530-3.
23. Hancock E, Osborne JP. Vigabatrin in the treatment of infantile spasms in tuberous sclerosis: literature review. J Child Neurol. 1999;14:71-4.
24. Engel J Jr, McDermott MP, Wiebe S, et al. Early surgical therapy for drug-resistant temporal lobe epilepsy: a randomized trial. JAMA. 2012;307:922-30.
25. Jansen FE, van Huffelen AC, Algra A, van Nieuwnhuizen O. Epilepsy surgery in tuberous sclerosis: a systematic review. Epilepsia. 2007;48:1477-84.
26. Arya R, Tenney JR, Horn PS, et al. Long-term outcomes of resective epilepsy surgery after invasive presurgical evaluation in children with tuberous sclerosis complex and bilateral multiple lesions. J Neurosurg Pediatr. 2015;15:26-33.
27. Krsek P, Jahodova A, Kyncl M, et al. Predictors of seizure-free outcome after epilepsy surgery for pediatric tuberous sclerosis complex. Epilepsia. 2013;54:1913-21.
28. Fallah A, Guyatt GH, Snead OC 3rd, et al. Predictors of seizure outcomes in children with tuberous sclerosis complex and intractable epilepsy undergoing resective epilepsy surgery: an individual participant data meta-analysis. PLoS One. 2013;8:e53565.
29. Zhang K, Hu WH, Zhang C, Meng FH, Chen N, Zhang JG. Predictors of seizure freedom after surgical management of tuberous sclerosis complex: a systematic review and meta-analysis. Epilepsy Res. 2013;105:377-83.
30. Fallah A, Rodgers SD, Weil AG, et al. Resective epilepsy surgery for tuberous sclerosis in children: determining predictors of seizure outcomes in a multicenter retrospective cohort study. Neurosurgery. 2015;77:517-24.
31. Weiner HL, Carlson C, Ridgway EB, et al. Epilepsy surgery in young children with tuberous sclerosis: results of a novel approach. Pediatrics. 2006;117:1494-502.
32. Liu SY, An N, Yang MH, et al. Surgical treatment for epilepsy in 17 children with tuberous sclerosis-related West syndrome. Epilepsy Res. 2012;101:36-45.
33. Zaroff CM, Morrison C, Ferraris N, Weiner HL, Miles DK, Devinsky O. Developmental outcome of epilepsy surgery in tuberous sclerosis complex. Epileptic Disord. 2005;7:321-6.
34. Rosser T, Panigrahy A, McClintock W. The diverse clinical manifestations of tuberous sclerosis complex: a review. Semin Pediatr Neurol. 2006;13:27-36.
35. Castillon-Benavides NK, Salinas-Lara C, Ponce-Guerrero F, Leon P, Gelista N, Tena-Suck ML. Tuberous sclerosis complex and sphenoid meningioma. Arq Neuropsiquiatr. 2010;68:455-8.
36. Nandagopal R, Vortmeyer A, Oldfield EH, Stratakis CA. Cushing's syndrome due to a pituitary corticotropinoma in a child with tuberous sclerosis: an association or a coincidence? Clin Endocrinol. 2007;67:639-41.
37. Boronat S, Caruso P, Auladell M, Van Eeghen A, Thiele EA. Arachnoid cysts in tuberous sclerosis complex. Brain Dev. 2014;36:801-6.

38. Hinton RB, Prakash A, Romp RL, Krueger DA, Knilans TK. Cardiovascular manifestation of tuberous sclerosis complex and summary of the revised diagnostic criteria and surveillance and management recommendation from the international tuberous sclerosis consensus group. J Am Heart Assoc. 2014;3:e001493.

39. Sciacca P, Giacchi V, Mattia C, et al. Rhabdomyomas and tuberous sclerosis complex: our experience in 33 cases. BMC Cardiovasc Disord. 2014;14:66.

40. Korula S, Ekbote A, Kumar N, Danda S, Agarwal I, Chaturvedi S. Renal manifestations of tuberous sclerosis among children: an Indian experience and review of the literature. Clin Kidney J. 2014;7:134-7.

41. Dixon BP, Hulbert JC, Bissler JJ. Tuberous sclerosis complex renal disease. Nephron Exp Nephrol. 2011;118:e15-20.

42. Rowley SA, O'Callaghan FJ, Osborne JP. Ophthalmic manifestations of tuberous sclerosis: a population based study. Br J Ophthalmol. 2001;85:420-3.

43. Scully C. Orofacial manifestations in tuberous sclerosis. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1977;44:706-16.

44. Hoshiai S, Oguma E, Sato Y, Konishi T, Minami M. Congenital focal lymphedema as a diagnostic clue to tuberous sclerosis complex: report of two cases diagnosed by ultrasound. Skeletal Radiol. 2015;44:1165-8.

45. Bolton PF, Park RJ, Higgins JN, Griffiths PD, Pickles A. Neuro-epileptic determinants of autism spectrum disorders in tuberous sclerosis complex. Brain. 2002;125:1247-55.

46. Cusmai R, Moavero R, Bombardieri R, Vigevano F, Curatolo P. Long-term neurological outcome in children with early-onset epilepsy associated with tuberous sclerosis. Epilepsy Behav. 2011;22:735-9.

47. D'Agati E, Moavero R, Cerminara C, Curatolo P. Attention-deficit hyperactivity disorder (ADHD) and tuberous sclerosis complex. J Child Neurol. 2009;24:1282-7.

48. de Vries PJ, Whittemore VH, Leclezio L, et al. Tuberous sclerosis associated neuropsychiatric disorders (TAND) and the TAND checklist. Pediatr Neurol. 2015;52:25-35.

49. Robins DL, Casagrande K, Barton M, Chen CM, Dumont-Mathieu T, Fein D. Validation of the modified checklist for Autism in toddlers, revised with follow-up (M-CHAT-R/F). Pediatrics. 2014;133:37-45.

50. Canadian Attention Deficit Hyperactivity Disorder Resource Alliance (CADDRA): Canadian ADHD Practice Guidelines, Third Edition, Toronto ON; CADDRA, 2011.

51. Goodman A, Goodman R. Strengths and difficulties questionnaire as a dimensional measure of child mental health. J Am Acad Child Adolesc Psychiatry. 2009;48:400-3.

52. Varni JW, Seid M, Knight TS, Uzark K, Szer IS. The PedsQL 4.0 Generic Core Scales: sensitivity, responsiveness, and impact on clinical decision making. J Behav Med. 2002;25: 175-93.