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Original Article

Trend of seizure remission in patients with tuberous sclerosis complex: A retrospective medical review

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Abstract

Background: Seizures in tuberous sclerosis complex (TSC) tend to be intractable over time and become a subsequent psychological burden for the patients. The purpose of the current study was to describe the onset, phenotype, and factors associated with seizure remission in patients with TSC.

Methods: Patients diagnosed with TSC between 2009 and 2015 completed a questionnaire interview and underwent a systematic evaluation, including a medical review of their epilepsy history and neurobehavioral disorder assessment.

Results: Of the 61 patients, 50 patients (82.0%) had a positive seizure history. The active (n = 34) and seizure remission (n = 16) groups showed significant differences in age, neurobehavioral disorder, history of refractory epilepsy, and onset age ($p < 0.001$, $p < 0.05$, $p < 0.05$, and $p < 0.05$, respectively). The remission rates were 33.3% and 38.5% for those aged 6–18 years and over 18 years, respectively (p for trend = 0.01).

Conclusion: Seizure remission can occur in adulthood. It shows a high correlation with patient age, minor refractory epilepsy, and neurobehavioral disorders.

Keywords: Refractory epilepsy; Seizure remission; Tuberous sclerosis complex

1. Introduction

Seizures in tuberous sclerosis complex (TSC) tend to become medically refractory over time. Several reports have speculated that cortical tubers in TSC are potentially epileptogenic. Cortical tubers consist of dysplastic neurons and glial cells that distort the normal cortical architecture, causing them to be highly epileptogenic.[1,2] Nearly 60% of patients with TSC seizures experienced its onset during infancy. In pediatric patients with TSC, the likelihood of developing epilepsy is estimated to be 80–90%.[3] These neurological comorbidities are usually a huge psychological burden on caregivers because of the life-long course of treatment.[4]

The condition of epileptogenic foci usually causes seizures in infancy. The discontinuation of antiepileptic drug (AEDs) is

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not recommended because permanent intracranial lesions, particularly cortical tubers, are highly associated with epilepsy.[5] AEDs remain the primary treatment modality, with many patients developing medical refractory epilepsy because of permanent epileptic foci. Yet, there is often a bias among physicians to continue epilepsy treatment, even after an individual has exhibited sustained seizure remission.[6] Although there are numerous studies on TSC-related epilepsy, there is limited information on the seizure course and remission in patients with TSC. Clinical follow-up and awareness of potential comorbidities may be needed to minimize psychological burden.

Therefore, the current study aimed to examine various aspects of TSC seizures, including the onset, phenotype, age of seizure remission, and associated factors from childhood to adulthood.

2. Methods

The study uses a cross-sectional design, although a longitudinal study design would have been preferable. Patients diagnosed with TSC were systematically evaluated from 2009 to 2015 at the Integrated Clinic for TSC in a single medical center. Given the retrospective design, all patients underwent a medical review. All patient diagnoses were confirmed using the Roach's Clinical Diagnostic Criteria[7] or the 2012 International TSC Consensus Conference Guidelines.[8] The patients were either previously evaluated at the Integrated Clinics or referred by the Taiwan Tuberous Sclerosis Complex (TTSC, http://www.ttsc.org.tw/) for medical consultation.

During their visit to the Integrated Clinic for TSC, patients underwent a systematic evaluation and questionnaire interview, including a medical review of the history of their epilepsy and a neurobehavioral disorder assessment. Patients diagnosed of TSC prior to onset of seizures were closely surveyed and received early treatment for seizures to reduce refractory epilepsy. Refractory epilepsy was defined as the being diagnosable when a patient failed to become seizure free with adequate trials of two AEDs. Patients were considered seizure free/in remission if they were without clinical seizures for at least 1 year, using the last clinical visit documenting seizure status as the end-point of follow-up.[9] Epileptic syndromes included infantile spasm (IS) and Lennox-Gastaut syndrome (LGS), and seizure phenotypes were recorded as generalized seizures (i.e., tonic-clonic, tonic, clonic, myoclonic, and atonic) or partial seizures (i.e., complex partial and simple partial).[10] Neurobehavioral comorbidities, including intellectual disability (ID), developmental delay (DD), or autism spectrum disorder, were assessed by clinical psychologists according to Diagnostic and Statistical Manual of Mental Disorders.

The patients were evaluated using routine brain magnetic resonance imaging (MRI) or computed tomography (CT) scanning. Subependymal giant cell astrocytoma (SEGA) was defined as being present when hamartomas, which arose at the caudothalamic groove adjacent to the foramen of Monro or a subependymal lesion at any location, and had serial growth on consecutive imaging, were observed, regardless of size. Subependymal nodules (SENs) were taken to be present when small asymptomatic protrusions into the walls of the lateral ventricles were observed.

2.1. Statistical analysis

Non-parametric data were assessed with the Mann−Whitney U test and expressed as medians and ranges. The chi-square test or Fisher's exact test were used to compare categorical variables. Different age groups for trends in seizure remission, neurobehavioral disorders, and refractory epilepsy were analyzed using the Cochran-Armitage trend test. Statistical significance was set at $p < 0.05$. All statistical analyses were conducted using SAS 9.4 and SPSS for Windows, Version 18.0 (SPSS Inc., Chicago, IL).

3. Results

A total of 61 patients with TSC (26 male and 35 female patients; aged 1 month to 68 years) were enrolled. Patients were grouped into age ranges as follows: <6 years (n = 17), 6−18 years (n = 18), and >18 years (n = 26). A total of 50 of the 61 patients (82.0%) had a positive seizure history, of whom 34 patients (55.7%) were active and 16 patients (26.2%) were in remission/seizure-free. Intracranial lesions were investigated using either MRI (56 patients) or CT (8 patients). Intracranial lesions, SENs, and SEGAs were revealed in 42 patients (75.0% of 56 by MRI) exhibiting cortical tubers, 51 patients (83.6%), and 10 patients (16.4%), respectively. Four underwent surgery due to SEGA subsequent obstructive hydrocephalus. Of neurobehavioral disorders, 31 patients (50.8%) had ID/DD, while 6 patients (9.8%) were on the autistic spectrum (Table 1).

Table 2 outlines the factors associated with being in remission/seizure-free. When comparing the groups of active (n = 34) and remission/free (n = 16) patients, there were no statistically significant differences in intracranial lesions, including cortical tubers, SENs, or SEGAs. There were, however, significant differences in age, neurobehavioral disorders, and history of RE ($p < 0.001$, $p<0.05$, and $p<0.05$, respectively). Of the seizure phenotypes, partial seizure was the most common phenotype, which was seen in 41 patients (82.0%). It was correlated with active seizures ($p<0.05$). The ages of seizure onset were recorded as <1 year, 1−6 years, and >6 years, in 26 (52.0%), 20 (40.0%), and 4 (8.0%) patients, respectively. When the age group distributions were compared, 62.5% of patients aged 1−6 years were in remission/seizure-free ($p < 0.05$). When the AED numbers between the active group and remission/free group were compared, there were 26 (76.5%) patients with ≥2 AEDs in the former and 8 (57.1%) patients with ≤1 AED in the latter ($p < 0.05$).

Table 3 outline the trends of the remission/seizure-free group. The <6 year group was compared as the baseline with the groups aged 6−18 years and >18 years. The remission rate trends were 33.3% and 38.5% in those aged 6−18 years and >18 years, respectively (p for trend<0.01).

Table 1
Demography data of TSC patients, n = 61.

Variable	Numbers	(%)
Gender		
Male	26	42.6
Female	35	57.4
Age		
<6	17	27.9
6−18	18	29.5
>18	26	42.6
Genetic analysis		
TSC1	11	18.0
TSC2	29	47.5
NMI/ND	21	34.4
Seizure history		
No	11	18.0
Yes	50	82.0
AED numbers (n = 48)		
1	16	29.2
2	14	23.0
3	11	18.0
4	5	8.2
5	2	3.3
Seizures Outcome		
Active	34	55.7
Remission	16	26.2
Intracranial lesions		
Cortical tubers (MRI)	42/56	75.0
SENs	51	83.6
SEGAs (>1 cm)	10	16.4
Neurobehavioral disorders		
ID/DD	43	70.5
Autistic spectrum	9	14.6

RE = refractory epilepsy; MRI = magnetic resonance image; SEGA = subependymal giant cell astrocytoma; SENs = subependymal nodules; MR = intellectual disability, DD = Developmental delay. NMI = no mutation identified, ND = not done. AED = antiepileptic drug.

Table 2
The factors of seizures remission in TSC patients. n = 50.

Variable	Seizures (%)			p
	All	Active	Remission/free	
Numbers	50	34	16	
Patient's age (year)	15 (0.5−68)	6 (0.5−36)	19 (10−68)	<0.001***
Cortical tubers (MRI)	37/49 (75.5)	26/33 (78.8)	11 (75.0)	0.245
SENs	43 (86)	30 (88.2)	13 (81.25)	0.396
SEGAs	7 (14)	4 (11.7)	3 (18.75)	0.396
Genetic analysis				
TSC1	9	6	3	0.583
TSC2	25	18	7	
Neurobehavioral disorders	39 (78)	30 (88.2)	9 (56.3)	0.05*
History of RE	20 (40.0)	19 (55.9)	1 (6.3)	<0.001***
Epileptic syndromes				
IS/LGS	24 (48.0)	17 (50.0)	7 (43.7)	0.680
Seizure phenotype				
Generalized	23 (46.0)	12 (35.3)	11 (68.8)	<0.05*
Partial	41 (82.0)	31 (91.2)	10 (62.5)	<0.05*
Age of seizure onset (year)				<0.05*
<1	26 (52.0)	20 (58.8)	6 (37.5)	
1−6	20 (40.0)	10 (29.4)	10 (62.5)	
>6	4 (8.0)	4 (11.7)	0	
AED numbers (n = 48)		N = 34	N = 14	
≦1	16 (33.3)	8 (23.5)	8 (57.1)	<0.05*
≧2	32 (66.7)	26 (76.5)	6 (42.9)	

*$p < 0.05$,***$p < 0.001$.
Data are shown as medians (ranges) or number (percentage); MRI: magnetic resonance imaging; SEGA: subependymal giant cell astrocytoma; SENs: subependymal nodules.
Neurobehavioral disorders includes mental retardation and autistic spectrum disorders.
RE = refractory epilepsy, IS= Infantile spasm; LGS = Lennox-Gastaut syndrome. AED = antiepileptic drug.

Table 3
Seizure and neurobehavioral disorders in different age groups. n = 61.

Group (Age, years)	<6	6−18	>18,	p[a]
Numbers (%)	17	18	26	
Seizures				
None	0	3 (16.7)	8 (30.8)	<0.01**
Active	17 (100.0)	9 (50.0)	8 (30.8)	<0.0001***
Remission	0	6 (33.3)	10 (38.5)	<0.01**

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.
[a] Cochran-Armitage trend test.

4. Discussion

The present study combined the retrospective review of clinical data with routine neuroimaging for TSC. These results highlighted the trend and factors associated with patients with TSC, from childhood to adulthood, who are in remission/seizure-free. The data describe trends in epilepsy severity over time in patients with TSC as they age. It provides novel and interesting data on the rates of remission of seizures with aging, and the factors that predict this, from a TSC clinic cohort that span pediatric and adult ages. The data is important for clinicians who need to manage epilepsy in patients with TSC.

Although epilepsy in TSC can be difficult to control, some limited studies present factors associated with seizure remission. In the generalized population, seizure remission is associated with normal cognition and lower burden of intracranial lesions, allowing patients to achieve discontinuation of AEDs after 2−3 years of medication.[11] A previous study with a cohort of 112 pediatric patients with TSC, revealed that 14.2% of the patients exhibited seizure remission of sufficient duration and character to permit a trial of AED discontinuation.[6] The current study included both pediatric and adult patients, and revealed a remission rate of 37% of all patients with TSC. By subgrouping, we were able to observe remission rates increasing with age, implying a trend of condition stabilization with the passage of time after adequate treatment.

It was previously reported that one-third of patients achieved epilepsy remission and appeared cognitively normal.[12] Despite limited case numbers, the current study displayed factors of seizure remission that were more closely associated with older age, minor neurobehavioral disorders, and lower rates of refractory epilepsy. In contrast, intracranial lesions with cortical tubers, SENs, and SEGAs were not

associated with seizure remission. In patients with TSC, numbers of cortical tubers were actually correlated with an individual's cognition and seizure severity.[13] However, since the current study focused on the prevalence of cortical tubers in variable groups, without a focus on detailed cortical tubers in each individual, there was no correlation between cortical tubers and the seizure remission rate. It is possible that individual variations in cortical tubers will alter the seizure condition.

Seizures associated with TSC are often refractory, carrying significant individual and societal impact. They are difficult to treat and interfere with normal cognitive and neuropsychiatric development. Of epileptic syndromes, IS and Lennox-Gastaut syndrome are significant risk factors for the development of medically refractory epilepsy.[3] In patients with TSC, refractory epilepsy is closely associated with global epilepsy development. In particular, cognitive disability is associated with a history of IS and refractory seizures. However, several studies have shown that some children with TSC and IS have normal cognitive outcomes, particularly if seizure control is achieved early.[1]

Similar to that in previous reports, the current data revealed that 52% of patients had seizures during infancy. Despite the strong propensity for patients with TSC to develop epilepsy in infancy, 8.0% of children over the age of 6 years without a history of epilepsy subsequently developed seizures, indicating a risk of developing epilepsy after reaching school age. The current data demonstrated that the age of epilepsy onset and ID correlated with active and remission/seizure-free. It is noteworthy that the incidences of neurobehavioral comorbidities and history of refractory epilepsy are higher in the active group. TSC1/TSC2 mutations, however, were not correlated with either group.[9,14] Treatment is a factor that influence the outcome of seizures and neurobehavioral disorders. If the first AED is not efficacious, then the outcome is less favorable, although many children will have remission of their epilepsy. Invasive or complex treatments for epilepsy with partial and generalized seizures should not be used, until at least two AEDs have failed to control seizures.[15]

Seizures in TSC are usually focal, arising from epileptogenic cortical tubers or from the epileptogenic area surrounding these tubers.[16] Of all the seizure phenotypes, partial motor and complex partial seizures, with or without secondary generalization are the most common, probably due to focal cerebral pathology.[17] The severity of seizures in TSC ranges from mild to catastrophic; intractable seizures with evidence of intracranial lesions or skin adenomas present during infancy.[18,19] The history of epilepsy in patients with TSC, from infancy into childhood, tends to be one with increasing seizure frequency and severity, poor response to AEDs, and diminished quality of life due to the adverse effects of the medication.[20]

Previous studies recognized that the cortical tuber count is a reliable biomarker for the severity of cerebral dysfunction, and demonstrated that better cognition function correlated with more successful treatment outcomes and longer periods of seizure remission.[14] The current results, however, highlight that imaging features (like cortical tubers, SEGAs, and SENs) are not helpful in distinguishing patients who are active and in remission/seizure-free. The striking feature associated with the remission/free group of patients with TSC was the onset of age. Further, the trend of seizure control in patients with TSC correlated with the age groups. Thus, the onset of epilepsy at an early age is one of the major risk factors for subsequent medical resistance, as previously confirmed.[21] The age-dependent trend of epilepsy was even observed in patients with characteristic intracranial lesions.

4.1. Limitations

The limitations of the present study include its retrospective, cross-sectional design and small sample size. Most of the patients were previously diagnosed and treated at other hospitals, before being referred to the integrated clinics for survey. In terms of factors predicting remission, multivariate analysis would be preferred, to ascertain the factors that were most strongly predictive of remission. Moreover, although it has been used in previous studies, the use of the term remission is not common. It is possible these patients could have been on medication at the time of clinical review and only required to have been seizure-free for 1 year. It is likely that a significant percentage of these patients would relapse if the medication was withdrawn. Missing or uncertain data were checked with the patients' parents because in many cases their treatment was initiated many years prior to the present study. Similarly, there could be a bias with selection of patients with particular seizure types or some special medical needs. The protocol for seizure control in patients who participated in the current study could have varied, subsequently influencing the treatment. However, there should be some information about the duration and severity of epilepsy and when the patients became seizure-free. Further, neither the number of AEDs nor periods of epilepsy of each patient was shown in the study. The likelihood of bias in the study is the fact that the younger patients (as young as 1 month) may not have had the time to reach remission.

In conclusion, seizures remain a main comorbidity in patients with TSC, particularly in pediatric patients. Although they tend to be highly intractable, seizures may become less severe with age. Seizure remission in patients with TSC can be expected in later childhood and adulthood. Achieving seizure remission is associated with an absence of neurobehavioral disorders and negative refractory epilepsy. Awareness of the potential trend of seizure course can substantially benefit in reducing the psychological burden when caring for children with TSC and refractory epilepsy.

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