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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).

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