Child's Nervous System (2019) 35:463–468
https://doi.org/10.1007/s00381-019-04066-7

ORIGINAL ARTICLE

Factors affecting epilepsy prognosis in patients with tuberous sclerosis

Gülen Gül Mert[1] · Şakir Altunbaşak[1] · Özlem Hergüner[1] · Faruk İncecik[1] · Hilal Cansever Övetti[1] · Neslihan Özcan[1] · Duygu Kuşçu[2] · İlker Ünal[3]

Received: 16 November 2018 / Accepted: 16 January 2019 / Published online: 23 January 2019

Abstract

Purpose We aimed to determine the characteristics of epileptic seizures that significantly affect the cognitive functions of 83 patients followed with tuberous sclerosis complex (TSC), their resistance to treatment and risk factors causing this resistance.

Materials-methods In order to determine the prognosis, the seizure-free/seizure-controlled group and the group with refractory seizures were compared. In addition, risk factors affecting cognitive functions in the patients were determined.

Results There was a statistical significance between the presence of a history of seizures in the neonatal period, the age of onset of seizures being less than 2 years of age, autism, status epilepticus, Lennox-Gastaut syndrome (LGS), presence of infantile spasm, generalization of the electroencephalography (EEG) findings, the number of tubers in cerebral imaging being more than three and refractory seizures ($p < 0.05$). Statistically significant relationship was found between presence of a history of seizures in the neonatal period, the age of onset of seizures, autism, LGS, presence of infantile spasm, presence of status epilepticus history, history of using more than three antiepileptic drugs, generalization of EEG findings, presence of SEGA in cerebral imaging, number of tubers being more than three and the patient's mental retardation ($p < 0.05$).

Conclusion In logistic regression analysis, the age of the seizure onset being less than 2 years of age, the presence of autism and number of tubers being more than three in cerebral magnetic resonance imaging (MRI) are determined to be the risk factors that most likely to increase the seizures to be more resistant.

Keywords Tuberous sclerosis · Epilepsy · Prognosis

Introduction

Tuberous sclerosis complex (TSC) is an autosomal dominant genetic disorder with an incidence of approximately 1 in 5000 to 10,000 live births that is characterized with pleomorphic features involving many organ systems, including multiple benign hamartomas of the brain, eyes, heart, lung, liver, kidney, and skin [1, 2]. It is caused by a mutation in either the TSC1 gene located on choromosome 9q34 encoding hamartin, or the TSC2 gene located on choromosome 16p13.3 encoding tuberin. Hamartin and tuberin form a heterodimer that suppresses the mTOR pathway which is important for regulating protein translation (in response to nutrition), cell cycle progression, and response to hypoxia [3, 4].

Most patients with TSC have epilepsy, and one half or more have cognitive deficits and learning disabilities; other common manifestations include autism, behavioral problems, and psychosocial difficulties. Epilepsy is one of the most frequent and significant causes of morbidity in TSC, affecting 79 to 90% of patients in population-based studies. Seizures begin in the first year of life in just over 60% of cases; however, patients with TSC remain at risk for new-onset seizures into adult life [5, 6].

Although many studies have been conducted on the prognosis of tuberous sclerosis complex, its association with cognitive functions and the factors that determine the prognosis are still not clearly defined. In this study, it was aimed to investigate the characteristics of epilepsy, which is an important cause of morbidity for patients with TSC, its resistance to treatment and risk factors demonstrating this resistance. Thus, patients can be led to epilepsy surgery or vagal nerve stimulation without losing

✉ Gülen Gül Mert
dr_gulen@hotmail.com

[1] Department of Pediatrics, Division of Pediatric Neurology, Cukurova University, Adana, Turkey

[2] Department of Psychology, Cukurova University, Adana, Turkey

[3] Department of Biostatistics, Cukurova University, Adana, Turkey

time and the factors affecting cognitive functions are defined.

Materials-methods

In this study, of the 91 patients who attended to Çukurova University Pediatric Neurology Department Outpatient Clinic between June 2015 and May 2017 diagnosed with tuberous sclerosis, 83 cases with at least 1 year of observation, regular file data and follow-up who meet TSC criteria were reviewed. The diagnosis of TSC was made according to the clinical diagnostic criteria, which was re-determined by the International Tuberous Sclerosis Complex Consensus Group in 2012 [7]. Eight patients were excluded from the study due to non-regular file data and follow-up. On June 1, 2018, under the decree no 72, ethic committee approval of the study from Cukurova University Faculty of Medicine Non-Interventional Clinical Trials Ethics Committee and consent from the families of the patients to participate in the study were obtained. Age of patients, gender, onset age of seizures, presence of consanguinity, presence of TSC disease in the family, presence of seizures in the neonatal period, seizure frequency in the last 1 year, seizure types, the number of antiepileptic drugs used, cerebral imaging findings, the number of tubers, EEG (electroencephalography) findings, the presence of behavior disorder, and results of intelligence tests were evaluated retrospectively. Expert Assessment of intelligence quotient (IQ) was conducted by clinical neuropsychologist using Stanford-Binet for children aged 2 to 6 years and WISC-R scale for children 6 years and older. The IQ value of 85 and above was considered as normal and under 70 was considered as mental retardation (American Psychiatric Association, 2000). Behavioral disorders were evaluated with results of at least two interviews by pediatric psychologist. Brain magnetic resonance imaging (MRI) was performed on all patients using 1.5 Tesla magnetic resonance device and evaluated by the radiology department. Seizure types were determined according to the 1981 ILAE classification [8]. All patients had interictal EEG records available for study. The recordings were obtained while younger children were in spontaneous or sedated sleep and the others were awake. Bipolar and reference montages were used. The recordings were examined for background activity and pathologic activities. Epileptic syndromes included infantile spasm (IS) and Lennox-Gastaut syndrome (LGS), and seizure phenotypes were recorded as generalized seizures or partial seizures. Patients were considered as the seizure-free/seizure-controlled group if they have not had clinical seizures for at least 1 year. Refractory (resistant seizure) was considered to have seizures once a month or more for at least 1 year, while using at least two antiepileptic drugs at the appropriate dose. To determine the prognosis and risk factors, seizure-free/seizure-controlled group was compared with the group with refractory seizures [9].

Statistical analysis

All analyses were performed using IBM SPSS Statistics Version 20.0 statistical software package. Categorical variables were expressed as numbers and percentages, whereas continuous variables were summarized as mean and standard deviation and as median and minimum-maximum, where appropriate. Chi-square test was used to compare categorical variables between the groups. The normality of distribution for continuous variables was confirmed with the Shapiro Wilk test. For comparison of continuous variables between two groups, the Student's *t* test or Mann-Whitney *U* test were used depending on whether the statistical hypotheses were fulfilled or not. Logistic regression analysis was performed to determine significant predictors of prognosis. In univariate analysis, variables significant at the $P < 0.25$ level were included in logistic regression analysis. The statistical level of significance for all tests was considered to be 0.05. (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.)

Results

Of the 83 patients with TSC, 40 (48.2%) were female and 43 (51.8%) were male. The mean age at patients' first admission to hospital was 33.52 ± 36.6 months (range 1–156 months), the mean age of onset of seizure was 25.46 ± 34.1 months (range 1–180 months), and the mean age at diagnosis was 18.8 ± 17.7 months (range 15 days–72 months), mean follow-up time was 102.8 ± 47.7 months (range 14–200 months). The mean age of the patients with refractory seizures was 135.76 ± 56.184 months, the mean age of onset of seizure was 9.94 ± 13.13 months and the mean age of seizure-free/seizure-controlled patients was 144.36 ± 49.7 months, and the mean age of onset of seizure was 35.70 ± 39.6 months. The most frequent reason for admission to the hospital was 59 (71.1%) seizures, 8 (9.6%) patients were admitted for developmental delay, 7 (8.4%) patients for marks on their bodies and 7 (8.4%) patients applied for diagnosis of rhabdomyoma on echocardiography in the neonatal period. One patient was diagnosed with TSC while hypertension etiology was investigated and one patient was diagnosed with TSC while supraventricular tachycardia etiology was investigated. There was no statistically significant difference between the seizure-free/seizure-controlled group and the group with refractory seizures in terms of presence of consanguinity, the presence of TSC disease in the family, the age at admission to the hospital, the presence of attention-deficit and hyperactivity disorder, the presence of subependymal nodule

(SEN), subependymal giant cell astrocytoma (SEGA) and white matter dysplasia in the cerebral MRI ($p > 0.05$). There was a statistically significant association between the presence of a history of seizures in the neonatal period, the age of onset of seizure being less than 2 years of age, presence of autism, status epilepticus, LGS, presence of infantile spasm, generalization of EEG finding, and tuber count of more than three in cerebral imaging and refractory seizures ($p < 0.05$) (Table 1).

In logistic regression analysis, age of onset of seizures, presence of autism, and tuber count of more than three in cerebral MRI were determined as risk factors that increase resistance of the seizures the most. Accordingly, the risk of seizures being refractory was increased by the presence of autism by 3.90-fold (95% Confidence Interval (CI) 1.11–13.73), by every 1-month reduction of onset age of seizures by 1.06-fold (95% CI 1.01–1.10 and tuber count more than three by 4.50-fold (95% CI 1.10–18.33) (Table 2).

The cognitive functions of the patients were evaluated according to the results of Intelligence Quotient test. Intelligence Quotient less than 70 was evaluated as mental retardation. Presence of a history of seizures in the neonatal period, age of seizure onset being less than 2 years of age, presence of autism, status epilepticus, LGS, presence of infantile spasm, presence of status epilepticus, history of using more than three antiepileptic drugs, generalization of EEG findings, presence of SEGA in cerebral imaging, tuber count more than three were statistically significantly associated with mental retardation in the patient ($p < 0.05$).

Discussion

Neurologic phenotype of TSC is highly variable, ranging from normal to severe, and consisting of refractory epilepsy, intellectual impairment, and psychiatric comorbidity. Central nervous system is affected in more than 90% of individuals with tuberous sclerosis, with the presence of pathological lesions [1].

The prevalence of epilepsy in patients with TSC has been reported as 93–96%. Nearly 80% of patients had seizure onset within the first 3 years of life [10]. In a study in the literature, it was reported that epilepsy control is difficult in patients with TSC, 1/3 of 291 patients were in remission and in 20% of them had refractory epilepsy. It was reported that patients in remission were monitored without medication and only 9.1% of them were relapsed [6]. In another study, 112 patients with TSC were evaluated and in 14.2% of them were reported to have seizure control [11]. In our study, 33 (39.8%) of the patients had no seizure control. Of the patients who had no seizure control, 8 (24.2%) had daily, 10 (30.3%) had weekly, 10 (30.3%) had monthly, and 5 (15.2%) had yearly seizures. C.J. Chu-Shore et al. reported that, of the 256 TSC patients who they evaluated, 73.2% of those who had mental retardation could not have seizure control [6]. In our study, 27 (82%) of the patients with refractory seizures have IQ values less than 70 and 6 of them (18%) have IQ values more than 70. Failure to control seizures significantly affects cognitive

Table 1 Statistical parameters of patient characteristics associated with epilepsy prognosis

Feature	Remission/free seizures		Refractor seizures		*p*
	n	%	*N*	%	
Sex					
Male	30	60	13	39.4	0.077
Female	20	40	20	60.6	
Parental consanguinity					
Yes	18	36.0	13	39.4	0.754
No	32	64.0	20	60.6	
TSC in family					
Yes	12	24.0	14	42.4	0.077
No	38	76.0	19	57.6	
Onset age of seizures					
< 2 age	25	50.0	30	90.9	*<0.001*
2–10 age	20	40.0	3	9.1	
> 10 age	5	10.0	0	0.0	
Neonatal seizure					
Yes	2	4.0	8	24.2	*0.012*
No	48	96.0	25	75.8	
IQ					
< 70	12	24	27	82	*<0.001*
> 70	38	76	6	18	
Infantile spasm					*<0.001*
Yes	6	12.0	15	45.5	
No	44	88.2	18	54.5	
LGS					
Yes	2	4.0	13	40.6	*<0.001*
No	48	96.0	19	59.4	
Autism					*<0.001*
Yes	7	14.0	21	63.6	
No	43	86.0	12	36.4	
ADHD					
Yes	16	32.0	9	27.3	0.646
No	34	68.0	24	72.7	
Status epilepticus					*<0.001*
Yes	4	8.0	17	51.5	
No	46	92.0	16	48.5	
AED numbers					
≤ 2	45	90.0	7	21.2	*< 0.001*
≥ 3	5	10.0	26	78.8	
EEG finding					
Normal	22	44.0	0	0.0	
Focal	18	36.0	5	15.2	*< 0.001*
Multifocal	6	12,0	6	18,2	
Generalized	4	8,0	22	66,6	
Cortical tubers					
< 3	25	50.0	4	12.1	*< 0.001*
> 3	25	50.0	29	87.9	
SEGA					
Yes	4	8.0	5	15.2	0.305
No	46	92.0	28	84.8	
SEN					
Yes	40	80.0	27	81.8	0.837
No	10	20.0	6	18.2	
White cell dysplasia					
Yes	2	4.0	5	15.2	0.108
No	48	96.0	28	84.8	

The italic emphasis of the values means statistically significance between the groups

Table 2 Risk coefficients of independent variables that affect epilepsy prognosis

Variable	Risk coefficient	95% CI	*p*
Autism	3.90	1.11–13.73	*0.034*
Onset age of seizures (every 1-month reduction)	1.06	1.01–1.10	*0.013*
Cortical tuber > 3	4.50	1.10–18.33	*0.037*

CI confidence interval

functions. While 21 (42%) of the patients whose seizure control was ensured had been discontinued on medication and are seizure-free for the last 1 year, 25 (50%) of them were seizure-free with single antiepileptic and 4 (8%) patients were seizure-free with multiple antiepileptic.

In the literature, early onset of seizure and presence of treatment-resistant IS seizures have been reported as important risk factors for refractory epilepsy developments in patients with TSC [6, 12]. In our study, one of the most important risk factors for the development of refractory epilepsy was detected to be early onset of seizure. Every 1-month decline in seizure onset age increased the development of refractory epilepsy by 1.06-fold. There was also a statistically significant relationship between the age of onset of seizures and mental retardation parallel with the literature.

In the literature, 36 children diagnosed with TSC were evaluated and the relationship between SE, IS, autism, and IQ score was investigated. A significant association was found between status epilepticus, IS, autism, and refractory epilepsy development, and IQ score was lower in these patients [13]. Several studies have shown that some children with TSC and IS have normal cognitive outcomes, particularly if seizure control is achieved early [14]. Preventative antiepileptic treatment may reduce the risk of mental retardation [15]. In our study, 21 (83%) of the 83 patients with TSC had a history of IS, and 6 of 21 patients (28.6%) had seizure control, 15 (71.4%) of them were being followed up due to refractory epilepsy. Nineteen of these patients had an IQ value less than 70. There was a statistically significant association between IS, LGS, SE, mental retardation, and refractory epilepsy. Fourty-eight percent of the patients who had seizure control and are seizure-free had complex partial seizures, 44.0% of then had simple partial seizures, 2.0% had IS, 6.0% had LGS. In accordance with the literature, patients with focal seizures had better prognosis and cognitive functions.

Individuals with TSC2 mutations have more tubers, an earlier age at seizure onset, and more intractable seizures than those with TSC1 mutation or without mutation identified [16]. In the study conducted by A. Vignoli et al., sporadic patients with TSC have reported to have better prognosis of epilepsy [9]. A limitation of our study is the retrospective analysis of the cases, so that we were unable to do genotype-phenotype correlation in patients with TSC.

The central nervous system findings of patients with TSC include cortical tubers, subependymal nodules (SEN), subependymal giant cell astrocytoma (SEGA), and white matter heterotopia (dysplastic and dsymyelinated white matter). Unlike other tuberous sclerosis related complex lesions, postnatal new tuber does not form. Neoplastic transformation is not observed in the tubers and the tubers may be calcified over time. Subependymal nodules are formation which developed in the fetal life, located under the ependymal layer of the lateral ventricle and the third ventricle which are smaller than 1 cm. In 90% of patients with TSC, cerebral MRI is detected [17, 18]. The relationship between the number and location of cortical tubers detected by MRI and severity of seizures is still controversial [19, 20]. In their meta-analysis, Goodman et al. suggested that the number of tubers can be used as a biomarker for the development of refractory epilepsy and mental retardation [21]. In the literature, in a study evaluating 160 patients with TSC, a statistically significant association between the presence of more than 6 tubers, presence of SEN and SEGA, mental retardation and refractory epilepsy however, 43 of the 57 patients without seizures (75.4%) had more than six tubers. Therefore, they suggested that MRI findings are not always very important in determining the prognosis of epilepsy and that they should be evaluated as an auxiliary factor [9]. In our study, in accordance with the literature, more than three tubers increase epilepsy development risk by 4.50-fold (95% CI 1.10–18.33). There was no significant association between SEN, SEGA, and white cell dysplasia in terms of risk of refractory epilepsy. We think, as the number of tuber increases, seizure control becomes more difficult and the frequency of mental retardation and autism increases due to increased number of epileptic foci.

Autism and autistic behaviors, including hyperactivity, inattention, and self-injurious behavior, are common in children with TSC and can be a significant source of stress for parents and caregivers. In the literature, the frequency of behavior problems in patients with TSC has been reported to be 40–90%. Behavior problems are more common in patients with mental retardation or refractory seizures. While the frequency of autism/attention-deficit hyperactivity disorder is 1% in the general population, it is 17–61% people with TSC [22, 23]. Some studies have reported that temporal cortical tubers are associated with autistic findings [24]. There are also studies reporting that the number and location of tubers are not associated with autistic findings [25]. In our study, autism was present in 21 (63.6%) patients with refractory epilepsy. The presence of autism increased the risk of refractory epilepsy by 3.90-fold (95% Confidence Interval (CI) 1.11–13.73). Twenty-five (89.3%) of the 28 patients with autism had

more than three tubers in cerebral MRI. Patients without mental retardation did not have a history of autism. There was also a statistically significant association between the presence of autism and mental retardation. We think that the presence of autism is associated with refractory epilepsy development and mental retardation, and the high number of tubers increases the risk of autism. We believe that these findings are closely related to the quality and quantity of dysplastic regions in the brain. While seizure control was ensured in 32% of 25 patients who are on follow-up with attention-deficit hyperactivity, 27.3 of them were being followed up due to refractory epilepsy. There was no statistically significant association between ADHD, mental retardation, and refractory epilepsy development risk. The fact that the study has been performed retrospectively in a limited time and that genetic analyses have not been conducted to evaluate the prognosis of patients are the most important reasons that limits the study. Cognitive functions were evaluated at any time. Whether there was an improvement in cognitive function after treatment could not be shown. Seizure control and seizure-free were evaluated as the absence of seizures in the patients for the last 1 year. In the studies in the literature, the number of antiepileptic drugs used by the seizure-controlled group was reported differently. Prospective studies are required to show how many patients have relapsed after the discontinuation of drugs.

Conclusion

The age of onset of being less than 2 years of age, presence of autism, more than three tubers in the cerebral MRI seizure in patients with TSC are the most important risk factors for refractory epilepsy development. There is a significant association between mental retardation and early age of seizure onset, IS, history of LGS, presence of autism, generalization of EEG findings, presence of status epilepticus, receiving polytherapy.

Compliance with ethical standards

On June 1, 2018, under the decree no 72, ethic committee approval of the study from Cukurova University Faculty of Medicine Non-Interventional Clinical Trials Ethics Committee and consent from the families of the patients to participate in the study were obtained

Conflict of interest The authors declare that they have no conflict of interest.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

1. Curatolo P, Bombardieri R, Jozwiak S (2008) Tuberous sclerosis. Lancet 372:657–668
2. Hallett L, Foster T, Liu Z, Blieden M, Valentim J (2011) Burden of disease and unmet needs in tuberous sclerosis complex with neurological manifestations: systematic review. Curr Med Res Opin 27: 1571–1583
3. Kwiatkowski DJ, Manning BD (2014) Molecular basis of giant cells in tuberous sclerosis complex. N Engl J Med 371:778–780
4. Child ND, Benarroch EE (2014) mTOR: its role in the nervous system and involvement in neurologic disease. Neurology 83: 1562–1572
5. Yates JR, Maclean C, Higgins JN et al (2011) The tuberous sclerosis 2000 study: presentation, initial assessments and implications for diagnosis and management. Arch Dis Child 96:1020–1025
6. Chu-Shore CJ, Major P, Camposano S et al (2010) The natural history of epilepsy in tuberous sclerosis complex. Epilepsia 51: 1236–1241
7. Northrup H, Krueger DA (2013) International tuberous sclerosis complex consensus group. Tuberous sclerosis complex diagnostic criteria update: recommendations of the 2012 international tuberous sclerosis complex consensus conference. Pediatr Neurol 49:243–254
8. Shinnar S (2010) The new ILAE classification. Epilepsia 51:715–717
9. Vignoli A, La Briola F, Turner K, Scornavacca G, Chiesa V, Zambrelli E et al (2013) Epilepsy in TSC: certain etiology does not mean certain prognosis. Epilepsia 54:2134–2142
10. Jozwiak S, Shwarz RA, Janniger CK, Bielicka-Cymerman J (2000) Usefulness of diagnostic criteria of tuberous sclerosis complex in pediatric patients. J Child Neurol 15:652–659
11. Sparagana SP, Delgado MR, Batchelor LL, Roach ES (2003) Seizure remission and antiepileptic drug discontinuation in children with tuberous sclerosis complex. Arch Neurol 60: 1286–1289
12. Wang S, Fallah A (2014) Optimal management of seizures associated with tuberous sclerosis complex: current and emerging options. Neuropsychiatr Dis Treat 23:2021–2030
13. Shehata H, AbdelGhaffar HM, Nasreldin M, Elmazny A, Abdelalim A, Sabbah A, Shalaby N (2017) Clinical patterns and outcomes of status epilepticus in patients with tuberous sclerosis complex. Ther and Clin Risk Manag 13:779–785
14. Saxena A, Sampson JR (2015) Epilepsy in tuberous sclerosis: phenotypes, mechanisms, and treatments. Semin Neurol 35:269–276
15. Primec ZR, Stare J, Neubauer D (2006) The risk of lower mental outcome in infantile spasms increases after three weeks of hypsarrhythmia duration. Epilepsia 47:2202–2205
16. Camposano S, Greenberg E, Kwiatkowski D, Thiele EA (2009) Distinct clinical characteristics of tuberous sclerosis complex patients with no mutation identified. Ann Hum Genet 73:141–146
17. Mizuguchi M, Takashima S (2001) Neuropathology of tuberous sclerosis. Brain and Development 23:508–515
18. Goh S, Butler W, Thiele EA (2004) Subependymal giant cell tumors in tuberous sclerosis complex. Neurology 63:1457–1461
19. Chou IJ, Wong A, Wang HS, Chou ML, Hung PC, Hsieh MY, Chang MY (2008) Neuroimaging correlation with neurological severity in tuberous sclerosis complex. Eur J Paediatr Neurol 12:108–112
20. Soo MP, Yong JL, Yong JS, Yong OK, Yong JW (2011) Clinical progress of epilepsy in children with tuberous sclerosis: prognostic factors for seizure outcome. Chonnam Med J 47:150–154
21. Goodman M, Lamm SH, Engel A, Shepherd CW, Houser OW, Gomez MR (1997) Cortical tuber count: a biomarker indicating neurologic severity of tuberous sclerosis complex. J Child Neurol 12:85–90
22. Kopp CM, Muzykewicz DA, Staley BA et al (2008) Behavior problems in children with tuberous sclerosis complex and parental stress. Epilepsy Behav 13:505–510

23. Bolton PF, Park RJ, Higgins JN et al (2002) Neuroepileptic determinants of autism spectrum disorders in tuberous sclerosis complex. Brain 125:1247–1255
24. Bolton PF, Griffiths PD (1997) Association of tuberous sclerosis of temporal lobes with autism and atypical autism. Lancet 349:392–395
25. Walz NC, Byars AW, Egelhoff JC, Franz DN (2002) Supratentorial tuber location and autism in tuberous sclerosis complex. J Child Neurol 17:830–832