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Evaluation of the Relationship Between Cranial Magnetic Resonance Imaging and Epileptic Features in Tuberous Sclerosis Complex

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Abstract

Objective: Tuberous sclerosis complex is an inherited neurocutaneous disease that is characterized by pleomorphic features involving many organ systems, especially the brain. Neurological involvement occurs in approximately 90% of patients with tuberous sclerosis complex and includes epilepsy, intellectual disability, and autism. The aim of this study is to investigate the relationship between epileptic seizures and electroencephalographic features and neuroradiological findings in patients with tuberous sclerosis complex.

Methods: In this study, 29 patients who were followed up in the outpatient clinic were included. Clinical, demographic, and laboratory data of the patients were analyzed retrospectively from patient files and computer database. Data analyzed included demographic features, neuroimaging findings; electroencephalographic findings, and seizure history. The relationship between tuberous sclerosis complex-specific brain magnetic resonance imaging findings and features of epileptic seizures was compared.

Results: The median age of our patients was 8.5 years (range: 1.7-17.3), and female (n = 9) to male (n = 20) ratio was 1:2.2. Significant correlation was found between the total number of cortical tubers detected by brain magnetic resonance imaging and (1) onset of seizures under 1 year old (P = .044) and (2) drug-resistant epilepsy (P = .03). The examination of clinical and electroencephalographic features of the patients revealed hypsarrhythmia in any electroencephalography in 11 patients (37.9%), first seizure under 1-year-old in 20 patients (69%), 19 (65.5%) patients with seizures in the past year, drug-resistant epilepsy in 12 patients (41.4%), and status epilepticus in 6 patients (20.7%).

Conclusion: In this study, we tried to reveal the brain magnetic resonance imaging findings and clinical features of patients with tuberous sclerosis complex, which were observed to cause serious neurological complications.

Keywords: Childhood, EEG, epilepsy, tuber, tuberous sclerosis complex

Tuberosklerozlu Hastalarda Kranial Manyetik Rezonans Görüntüleme ile Epilepsi Bulgularının Değerlendirilmesi

Öz

Amaç: Tüberoskleroz kompleksi (TSK), başta beyin olmak üzere birçok organel sistemini tutabilen pleomorfik özelliklerle karakterize kalıtsal bir nörokutanöz hastalıktır. Epilepsi, zihinsel gerilik ve otizmi içerebilen nörolojik tutulum, TSK'lı hastaların yaklaşık %90'ında görülür. Bu çalışmanın amacı TSK tanılı hastalarda epileptik nöbetler ile elektroensefalografik (EEG) özelliklerin nöroradyolojik bulgular ile ilişkisini araştırmaktır.

Yöntemler: Çalışmaya 29 TSK tanılı hasta dahil edildi. Hastaların klinik, demografik ve laboratuvar verileri hasta dosyalarından ve bilgisayar veri tabanından geriye dönük olarak elde edildi. Veriler; demografik veriler, beyin görüntüleme bulguları, EEG bulguları ve nöbet öykülerini içermekteydi. Çalışmada, TSK'ye spesifik beyin manyetik rezonans inceleme (MRİ) bulguları ile epileptik özellikler karşılaştırıldı.

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Bulgular: Hastalarımızın ortanca yaşı (min-maks) 8.5 yıl (1,7-17,3), kadın/erkek oranı 20/9 (1:2,2) idi. Beyin MRİ ile saptanan toplam kortikal tüber sayısı ile (1) bir yaşın altında nöbet başlangıcı (P = ,044) ve (2) ilaca dirençli epilepsi (P = ,03) arasında anlamlı korelasyon bulundu. Herhangi bir EEG'de hipsaritmi 11 hastada (%37,9), ilk nöbetin 1 yaşın altında başlaması 20 hastada (%69), son bir yıl içinde nöbet geçirme öyküsü 19 hastada (%65,5), ilaca dirençli epilepsi 12 hastada (%41,4) ve status epilepticus 6 hastada (%20,7) gözlendi.

Sonuç: Bu tek merkezli çalışmada ciddi nörolojik komplikasyonlara neden olduğu gözlenen TSK'lı hastaların kraniyal MRİ bulguları ve klinik özellikleri ortaya koymaya çalışıldı.

Anahtar Kelimeler: Çocukluk çağı, tüber, EEG, epilepsi, tüberoskleroz kompleksi

Tuberous sclerosis complex (TSC) is a familial, multisystem disease mainly characterized by intellectual disability, epilepsy, and facial adenoma sebaceum triad. It is one of the most common single gene disease and incidence in 1 in 1/6000-1/10 000 live births.[1] It is caused by a mutation of the TSC1 gene or the TSC2 gene, and most cases (80%) are de novo mutations. TSC2 mutation is approximately 4 times more common in de novo cases.[2] As a result of the mutation that occurs in the TSC1 (9q34) and TSC2 (16p13.3) genes, respectively, the formation of protein complexes of hamartin and tuberin is affected. Given the wide variety of organs affected by TSC, it is understood that TSC1 and TSC2 genes play an important role in regulating cell proliferation and differentiation.[3]

Neurological manifestations such as autism, intellectual disability, and epilepsy are seen in approximately 90% of TSC patients.[4,5] Epilepsy, one of the most common neurological findings in TSC, is a serious cause of morbidity. Most have seizures within the first year of life, although there are patients whose first seizures are delayed until adolescence or early adulthood. Infantile spasms occur in approximately 37% of children with TSC, and other seizure types are also seen in most patients over time. Infantile spasms are generally considered a sign of poor neurodevelopmental prognosis.[6,7]

Subependymal nodules, cortical tubers, and subependymal giant cell astrocytoma account for the most common lesions seen in the central nervous system.[8] There are several studies in the literature showing that the neurological status of TSC patients can be affected by the number, burden, and location of cortical tubers, and white matter lesions;[9-12] therefore, cranial magnetic resonance imaging (MRI) findings play an important role in determining the severity of seizures and poor neurodevelopmental prognosis. This study investigated the relationship between TSC-specific brain MRI findings and epileptic features in a group of TSC patients.

Methods

This study included 29 patients with TSC who were followed up at the Istanbul University-Cerrahpaşa Medical Faculty, Pediatric Neurology Outpatient Clinic. Patients who were followed up with the diagnosis of TSC in our outpatient clinic between 2014 and 2018 and who met the following criteria were included in the study.

1. Clinically diagnosed with TSC,[13]
2. Patients between 1 and 17 years of age,
3. Patients who had at least 1 year of follow-up, 1 wake–sleep video EEG, and 1 contrast-enhanced cranial MRI, and
4. Patients with complete demographic, clinical, and laboratory findings.

Patients with different neurological or psychiatric disorders (head trauma, asphyxia, etc.) independent of TSC were excluded from the study.

Clinical, demographic, and laboratory data of these patients were analyzed retrospectively from patient files and computer database. Seizure history, electroencephalogram (EEG), and neuroimaging findings were noted. Age and gender parameters were recorded.

Neuroimaging findings were evaluated based on cranial MRI findings. All MRI examinations were performed on a 1.5 Tesla or 3 Tesla MR scanner using a standard protocol. The MRI protocol included sagittal T1-weighted, axial T2-weighted, coronal T2-weighted, FLAIR, diffusion-weighted, post-contrast T1-weighted sequences, and either of SWI or gradient-echo sequences. MRI interpretation was performed by 2 radiologists (A.K.K. and O.K.) who were blind to clinical findings. MRI examinations of patients closest to the age of 8 years were examined in order to obtain as uniform sample as possible. Brain MRIs from individuals younger than 12 months of age were not used because myelination was not advanced enough to measure tuber size and reliably detect radial migration lines (RML).

The number of cortical tubers and their hemispheric-lobar distribution, the total number of RML, the total number of subependymal nodules and their distribution were evaluated. Typical localization and size greater than 1 cm were used for the diagnosis of subependymal giant cell astrocytoma.[14] The data obtained after the evaluation were recorded in a standard form.

Clinical data were obtained by retrospective chart analyzes. Parameters such as age at onset of epilepsy, gender, presence of hypsarrhythmia on any EEG record, presence of seizures before the age of 1 year old, status epilepticus history, having a history of seizure in the past year, and drug-resistant epilepsy (continuation of seizures despite 2 or more antiepileptic drugs) were noted. Sleep and wake EEGs performed using the 10/20 international electrode placement system were evaluated.

The data were summarized using descriptive statistics. Categorical data were presented with n, % values, while continuous data were presented as median and minimum–maximum range. Fisher's exact test was used to compare the categorical data. The measurement data were examined using the Kolmogorov–Smirnov test for the normal distribution assumption. For the comparison of non-normally distributed measurement data, the Mann–Whitney U-test was used in areas where suitable. P values less than .05 were considered significant in all statistical analyzes. Statistical analysis was performed by using the SPSS Statistics 20.0 for Windows (SPSS Inc., Chicago, Ill, USA) program.

Written informed consent was obtained from all patients included in the study. The study was planned and conducted according to the ethical standards detailed in the Declaration of Helsinki. This study was approved by the institutional research Ethics Committee (Cerrahpasa Medical Faculty, Istanbul University-Cerrahpasa, 24.01.2018-209373).

Results

The median age of our patients was 8.5 years (1.7-17.3 years) with a female (n = 9)/male (n = 20) ratio of 1:2.2. The median age of seizure onset was 9 months (1-84 months). All patients had cortical tubers in our study, and the median number of total tubers was 27 (range: 2-57) on brain MRI. Twenty-six patients (89.7%) had subependymal nodules (SEN), and median number was 4 (range: 0-9), and all patients (100%) had RML and the median number was 3 (range: 1-11) on brain MRI. Of the 29 patients, 11 (37.9%) had cardiac rhabdomyoma, and 7 (21.4%) had shagreen patch. Seven patients (n = 28; 24.1%) had retinal hamartoma. The clinical and demographic data are shown in Table 1.

Brain MRI findings were compared in terms of genders. There were statistically significant differences between the total number of cortical tubers (P = .001) in the male patients (median: 30; range: 5-57) and female patients (median: 9; range: 2-27); between total SEN count (P = .008) in the male patients (median: 5; range: 0-9) and female patients (median: 2.5; range: 0-6); and also between total RML number (P = .023) in the male patients (median: 4; range: 1-11) and female patients (median: 2; range: 1-5).

When the epileptic features of the patients were examined, hypsarrhythmia in any EEG was observed in 11 patients (37.9), first seizure under 1-year-old in 20 patients (69%), 19 patients (65.5%) with seizures in the past year, drug-resistant epilepsy in 12 patients (41.4%), and status epilepticus was seen in 6 patients (20.7%). All the EEGs were normal in 4 patients (13.8%). The relationship between brain MRI findings and epileptic features plus EEG findings is shown in detail in Table 2.

Table 1. The Clinical, Demographic, and MRI Data (n = 29)

Age of study group (years), median (min-max)	**8.5 (1.7-17.3)**
Gender (male/female)	20/9
Age of seizure onset (months), median (min-max)	9 (1-84)
Cardiac rhabdomyoma, n (%)	11 (37.9)
Retinal hamartomas, (n = 28, %)	7 (21.4)
Shagreen patch, n (%)	7 (24.1)
Subependymal nodules, n (%)	26 (89.7)
Total tubers (n), median (min-max)	27 (2-57)
RML (n), median (min-max)	3 (1-11)
Total SEN (n), median (min-max)	4 (0-9)

EEG, electroencephalography; RML, radial migration lines; SEN, subependymal nodules; MRI, magnetic resonance imaging.

Discussion

Neurological symptoms, which are the main cause of morbidity and mortality in patients with TSC, have been reported in 85% of the patients. Epilepsy is one of the most common neurological symptoms with a prevalence of 62-93% in patients with TSC.[7,15] It has been reported that 99% of patients with a diagnosis of TSC presenting with seizures subsequently develop epilepsy and usually begins in the first year of life.[6] Likewise, in our TSC patient group, the median age of seizure onset was less than 1 year old (median: 9 months of age).

In this study, some differences were found between male and female gender in terms of brain MRI evaluation. Total cortical tuber, total SEN, and RML count were significantly higher in male gender. When the whole patient group was evaluated, a significant positive correlation was found between total tuber count in patients whose seizures started before the age of 1 year. Total cortical tuber count was also found to be higher in patients with drug-resistant epilepsy. These results may suggest that the disease course is more severe in the male gender. Likewise, meta-analyses of 2 large TSC studies showed more severe phenotypes in male patients in terms of cortical tubers, SEN, mental retardation, and seizure.[2,16] In this sense, the prediction we found in our study is quite compatible with relevant studies.

Seizures are the most common clinical manifestation of TSC. It has been reported that the most common seizure types in this disease are infantile spasm and partial seizures. Infantile spasm, the most common seizure type at the time of initial diagnosis, is seen in 36%-69% of patients.[17] On the other hand, TSC is the underlying cause of a quarter of all infantile spasm cases.[18] In accordance with the literature, we found a similar frequency of infantile spasm in our study (36.6%). Although total tuber count was found to be higher in cases with hypsarrhythmia in any of the EEGs (P = .084), a statistically significant difference was found only between left hemisphere tuber count and hypsarrhythmia (P = .028).

Neuroradiological findings such as the size of the tuber, the high number of tuber, and the high tuber/total brain volume ratio are associated with more resistant epilepsy and early age onset, as well as intellectual impairment.[9,19] Likewise, patients whose first seizure started under the age of 1 were significantly found to have a higher total number of tubers. Similarly, a similar relationship was found between our patients with drug-resistant epilepsy and the total number of tubers. Various studies have shown that patients with TSC2 mutations have a higher total tuber count and a higher incidence of neurological complications such as resistant seizures.[20,21] Although TSC is a neurocutaneous disease involving many organs with benign hamartomas, the brain is generally responsible for morbidity and mortality.

In this study, which we conducted with a limited number of patients, we tried to reveal the neuroradiological, clinical, and EEG features of TSC. Most of our findings in our study, which determined a more severe disease clinic especially in male gender, were found to be compatible with the literature. In the future, more detailed results will give much more

Table 2. The Relationship Between Brain MRI Findings and Epileptic Features

		n	Number of Total Tubers, Median (Min-Max)	P[a]	Number of Right Hemisphere Tubers Median (Min-Max)	P[a]	Number of Left Hemisphere Tubers Median (Min-Max)	P[a]	Number of RML, Median (Min-Max)	P[a]	Number of Total SEN, Median (Min-Max)	P[a]
Hypsarrhythmia in EEG	+	11	29 (9-57)	.084	12 (4-27)	.146	16 (4-29)	**.028**	5 (1-7)	.204	4 (2-9)	.521
	–	18	18 (2-35)		8 (0-20)		9 (2-19)		2.5 (1-11)		4 (0-7)	
Status epilepticus	+	6	30.5 (15-46)	.08	15.5 (6-24)	.102	16 (9-22)	**.041**	4 (2-5)	.278	5.5 (2-9)	.278
	–	23	18 (2-57)		8 (0-27)		10 (2-29)		2 (1-11)		4 (0-7)	
Seizure under 1-year of age	+	20	28 (2-57)	**.044**	12.5 (0-27)	**.03**	15 (2-29)	.069	4 (1-11)	0.077	4.5 (0-9)	.095
	–	9	15 (5-31)		6 (1-15)		9 (2-17)		2 (1-4)		3 (0-6)	
Drug-resistant epilepsy	+	12	30.5 (9-57)	**.03**	15.5 (4-27)	**.043**	15.5 (4-29)	**.038**	4 (1-7)	.14	3.5 (2-9)	.913
	–	17	18 (2-34)		8 (0-20)		10 (2-17)		2 (1-11)		4 (0-7)	
Seizure last 1-year	+	19	30 (9-57)	**.004**	14 (4-27)	**.005**	15 (4-29)	**.019**	4 (1-11)	.051	5 (2-9)	**.012**
	–	10	10.5 (2-30)		5.5 (0-15)		6 (2-16)		2 (1-5)		2.5 (0-6)	
EEG-normal	+	4	5.5 (2-15)	**.003**	2 (0-8)	**.004**	3.5 (2-7)	**.008**	1.5 (1-2)	**.03**	4.5 (0-7)	.927
	–	25	27 (6-57)		12 (3-27)		15 (2-29)		4 (1-11)		4 (0-9)	

[a]Mann–Whitney *U*-test.
EEG, electroencephalography; RML, radial migration lines; SEN, subependymal nodules.

illuminating results with more patient numbers and studies with molecular analysis.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of İstanbul University-Cerrahpaşa (Date: January 24, 2018, No: 209373).

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