DOI: 10.4274/tpa.116

Characteristics and the clinical prognosis of epilepsy in patients with a diagnosis of tuberous sclerosis complex

Sema Saltık[1], Elif Yüksel Karatoprak[1], Bülent Taşel[2]

[1]*Medeniyet University, Göztepe Education and Research Hospital, Pediatric Neurology Clinic, İstanbul, Turkey*
[2]*Medeniyet University, Göztepe Education and Research Hospital, Division of Radiology, İstanbul, Turkey*

Summary

Aim: Epilepsy is the most common neurological problem in tuberous sclerosis complex (TSC). The aim of this study is to investigate the clinical features and prognosis of epilepsy associated with TSC and to determine the factors that may affect the course of epilepsy in TSC patients.

Material and Method: Our study included 21 TSC patients (11/10: M/F) aged between 1-14 years (7.5±4.2) and followed up for 9 months-10 years because of epileptic seizures. After epileptic seizures were classified as seizures with good and poor prognosis, they were were statistically compared in terms of age at seizure onset, history of status and infantile spasms, initial treatment with vigabatrin, initial EEG findings, presence of autism or mental retardation or cognitive impairment, the number of cortical tubers and presence of astrocytoma.

Results: The age at seizure onset ranged between 3 days and 2.5 years. The most common seizure type in our patients was partial seizure and eight patients had infantile spasms and status epilepticus. As a result of follow-up, the prognosis was evaluated as poor in 11 and good in 10 patients. No statistical relationship was found between seizure prognosis and age at seizure onset (younger and older than 1 age), the history of status and infantile spasms, initial EEG findings, use of vigabatrin as the first drug, the presence of autism or mental retardation or cognitive impairment, the number and localization of cortical tubers and the presence of astrocytoma ($p>0.05$).

Conclusions: The prognosis of epilepsy in patients with TSC varies in each patient depending on several factors. For this reason close follow-up of these patients with clinical evaluation and EEG is required. *(Turk Arch Ped 2013; 48: 123-130)*

Key words: Epilepsy, prognosis, tuberous sclerosis complex

Introduction

Although many organs are affected in tuberous sclerosis complex (TSC), the most commonly involved organs include the brain, retina, kidneys, heart and skin (1,2,3,4). The diagnosis is made according to the diagnostic criteria of Roach which were revised in 1988 (5) (Table 1).

Although tuberous sclerosis complex is characterized with the triad of mental retardation, epilepsy and adenoma sebaceum, this triad is found only in 1/3 of the patients (6). Epilepsy is the most common neurological disorder observed in patients with TSC. Any kind of epileptic seizure may be observed in tuberous sclerosis complex and these seizures are generally resistant to anti-epileptic treatment (7). The characteristics of epilepsy in tuberous sclerosis complex have not been described yet. Although there are some studies examining the clinical, electroencephalographic (EEG) and cranial MR findings affecting the prognosis of epilepsy, there is no consensus on this subject yet (8,9,10).

This study aimed to investigate the characterstics of epileptic seizures and the clinical prognosis and to examine the factors which may affect the prognosis of epilepsy in patients with a diagnosis of epileptic TSC.

Material and Method

The files of 32 patients followed up with a diagnosis of TSC in our Pediatric Neurology Clinic between January 2001 and January 2012 were examined retropectively and 21 epileptic (87.5%) TSC patients selected according the following criteria who could be reached by phone were included in the study. Patient selection criteria:

Address for Correspondence: Elif Yüksel Karatoprak MD., Medeniyet University, Göztepe Education and Research Hospital, Pediatric Neurology Clinic, İstanbul, Turkey
E-mail: elifyuksel2001@yahoo.com **Received:** 08.09.2012 **Accepted:** 12.27.2012

1. A diagnosis of TSC according to the diagnostic criteria of Roach (5)

2. Follow-up of at least 9 months with a diagnosis of epilepsy

3. Verbal approval by the family on phone call and reinformation given for missing data or presentation for examination

4. Completion of all demographic, clinical and laboratory information related with the patient.

Demographic and other data of the 21 patients (11/10: M/F) included in the study explained below were noted.

I-Characteristics of epilepsy: the age at the time of the first seizure and the type of the first seizure, seizure types, frequencies and durations observed in the follow-up, history of presence of infantile spasm, antiepileptic drugs used in order.

II-The frequency of seizures was graded by dividing into 5 groups for the first and last year.

1. Very frequent: once a week or more often
2. Frequent: once a week-one a month
3. Moderately frequent: once a month-once in three months
4. Rare: less frequent than once in three months
5. Controlled: no seizure in the last 18 months.

III- The seizure prognosis was divided into two categories as good and poor prognosis. Good prognosis: rare or controlled seizure in recent years; poor prognosis: very frequent, frequent, moderately frequent seizures in recent years or presence of status even if seizures were rare.

IV- Electroencephalogram: Two sleep/wake EEGs including at least one-hour sleep for each patient were re-assessed by the same pediatric neurologist. EEG was performed again in the patients who did not have an EEG in the last one year. EEGs were divided into three groups according to presence of epileptic activity; the first group: epileptic activity is present, the second group: focal or diffuse epileptic activity is present, the third group: multiofocal epileptic activity or hypsarhythmia is present.

If focal epileptic activity was present in at least one EEG, it was noted for each patient and three groups were constituted according to the location of focal activity; the first group: focal epileptic activity is in the right hemisphere, the second group: focal epileptic activity is in the left hemisphere, the third group: no focal epileptic activity.

V-Cranial MR imaging: A total of 52 contrast cranial MR imagings beloning to 21 patients were reassessed by the same radiologist. Presence of cortical tubers, their numbers and localization, if present, presence of subependimal nodule, astrocytoma, heterotopy and white matter involvement and other characteristics, if present were recorded. A cortical tuber number above 12 was considered “plentiful”. If the cortical tubers showed density in a certain hemisphere, the predominant hemisphere was specified separately.

The intellectual or cognitive development levels of the patients were evaluated by age-appropriate psychometric tests, pediatric psychiatric examination and results of disability reports given by health committees. Autism was diagnosed according to the DSM-IV-TR (“Diagnostic and Statistical Manual of Mental Disorders 4th edition text revision”) diagnostic criteria (11). WISC-R (Wechsler Intelligence scale for Children) was applied in children between the ages of 6 and 16 years in order to determine the intellectual levels (12,13). A total intellectual score above 70 was considered normal intellectual level. Children with retarded intellectual development were classified as mild mental retardation (total intellectual score: 69-50), moderate mental retardation (total intellectual score: 49-30) and severe mental retardation (total intellectual score: <29). Denver II developmental test (DDT) was applied to evaluate cognitive development in children aged 6 years and below (14). Children with

Table 1. Diagnostic Criteria in Tuberous Sclerosis Complex

Major findings	Minor findings
1. Cortical tuber	1. Hypopigemented patch in the retina
2. Subependimal nodule	2. Hamartomatous rectal polyp
3. Giant cell astrocytome	3. Bone cyst
4- Hypomelanotic macules (ash-leaf sign)	4. Radial migration line in the brain withe matter
5. Shagreen patch	5. Multiple pits in the enamel
6. Adenoma sebaceum (Angiofibroma in the face) or fibrous plaqua in the forehead	6. Gingival fibroma
7. Multiple retinal hamarthomas	7. Extra-renal hamartoma
8. Ungual or periungual fibromas	8. Confetti skin lesions
9. Rhabdomyoma	9. Multiple renal cysts
10. Lymphangiomatosis in the lung or renal angiomyolipoma	

Definite diagnosis: two major or one major + two minor criteria
Suspicious diagnosis: one major + one minor criteria
Possible diagnosis: one major or two minor criteria

retardation in the developmental milestones according to age were defined as developmental delay if the clinical evaluation was also compatible.

To determine the risk factors which may affect the prognosis of seizures the patients who were classified as good and poor prognosis groups were statistically compared in terms of the age of onset of seizures, a history of status, presence of infantile spasm, initial EEG findings, location of the epileptic activity on EEG, intellectual and cognitive development levels, the number and locations of cortical tubers and presence of astrocytoma.

The study was initiated after obtaining approval from the ethics committee of Medeniyet University, Göztepe Education and Research Hospital.

Statistical analyses were performed using SPSS 15,0 for Windows (SPSS Inc, Chicago, IL) program. The Chi-square test was used for comparison of categorical variables. A p value below 0,05 was considered significant.

Results

The ages of 21 patients included in the study ranged between 1 and 14 years (7.5±4.2 yıl) and outpatient follow-up times ranged between 9 months and 10 years (5.3±3.9 years). Consanguineous marriage was found in 8 patients (38%) and a known history of TSC was found in 7 patients (35%). When the cutaneous findings of the patients were evaluated, depigmented nevus was found in 20 patients (95.2%), adenoma sabaceum was found in 14 patients (66.6%), fibrous plaqua in the forehead was found 5 patients (23.8%) and “Shagreen” patch was found in 4 patients (19%). Among other findings of the disease, rhabdomyoma in the heart was found in 3 patients (14.3%) and retinal astrocytoma was found in one patient (4.7%). When 7 patients (33.3%) who had renal involvement were examined, renal angiomyolipoma was found in five (23.8%) and renal cyst was found in two (9.5%).

When DSM-IV psychiatric assessments and intellectual or developmental tests of the patients were examined, it was found that 12 patients (57.1%) had an intellectual or cognitive development below normal and two patients (9.5%) had autism (Table 2).

Epilepsy characteristics: The age of onset of seizures ranged between the newborn period and 2,5 years of age and was mostly below the age of one (76.1%). Three patients had seizures in the newborn period (14.2%). The first seizure was partial in 9 patients (42.8%), diffuse tonic-clonic in 6 patients (28.5%), infantile spasm in 5 patients (23.8%) and atonic in one patient (4.7%). It was observed that 7 of these seizures (33%) developed during a period of fever. In the follow-up, partial seizures were observed in 20 of the patients (95.2%), infantile spasms were observed in 8 patients (38%), diffuse tonic-clonic seizures were observed in three patients (14.2%), atonic seizures were observed in three patients (14.2%) and absence seizures were observed in one patient (4.7%). Although status epilepticus developed during the clinical course in 8 of the patients (38%), it was found that seizures lasted shorter than 5 minutes in the majority of the patients (16 patients (76.1%)) .

When epilepsy treatments of the patients were examined, it was found that three patients used drugs other than vigabatrin throughout the follow-up and one of these patients was using carbamazepine and the other two patients were using carbamazepine plus valproic acid. While valproic acid was used in 8 of the patients as the initial antiepileptic drug, phenobarbital was used in 6 patients and vigabatrin was used in 6 patients as the initial drug. In three of the patients, epileptic seizures were under control with monotherapy throughout the follow-up period. Our only patient in whom drug treatment was discontinued is being followed up without seizure for one year since the discontinuace of treatment.

Electroencephalogram findings: While no epileptic activity was found on EEG in five (23.8%) of our patients, partial epileptic activity was found in 14 patients (66.6), hypsarhythmia was found in 8 patients (38%), diffuse epileptic activity was found in 2 patients (9.5%) and

Table 2. Distribution of the patients with a diagnosis of tuberous sclerosis according to presence of autism and intellectual-cognitive development levels

Autism/intellectual-cognitive development level	Number of patients	%
Autism (-) / normal	7	33.3
Autism (+)	2	9.5
Autism (-) / *growth retardation (+)	3	14.2
Autism (-) / *mental retardation (+)	9	42.8
Mild mental retardation	4	
Moderate mental retardation	2	
Severe mental retardation	1	

*For patient below the age of 6

**For patients aged 6 years and older

multifocal epileptic activity was found in 2 patients (9.5%) (Table 3).

Cranial MR imaging findings are given in Table 3. Cortical tuber was found in 20 patients (95.2%), subependimal nodule was found in 18 patients (85.7%), astrocytoma was found in 5 patients (23.8%) and white matter involvement was found in 2 patients (9.5%). Heterotopy was not observed in any patient.

The seizure prognosis was considered as poor in 11 of the patients and good in 10. Although seizures occured rarely in three of the patients, the seizure prognosis was considered poor, since status which led to monitoring in the intensive care unit occured. However, presence of status was not found to be a risk factor for poor prognosis. In patients who had infantil spasms, the epileptic seizure prognosis was observed to be poorer, but this difference was not statistically significant. No statistically significant difference was found between the patients whose age of the onset of seizures was one year and younger and above one year in terms of the prognosis of epilepsy. Initial EEG findings, the number of cortical tubers on cranial MR imaging, tubers being bilateral or regional and presence of astrocytoma had no effect on the prognosis of epilepsy. While frequent complex partial seizures continued in 2 of 5 patients who had astrocytoma, the seizures occured as status in one patient. In two patients the seizures had a good prognosis. No difference was found between the patients who were found to have autism or cognitive developmental-intellectual retardation and the patients who had no autism and whose cognitive developmental-intellectual development were normal in terms of the prognosis of epileptic seizures (Table 4).

Discussion

The most common neurological finding in tuberous sclerosis complex is epilepsy which has been reported with a rate of 80-90% (7,15,16,17,18,19,20). Although presence and prognosis of seizures in patients with tuberous sclerosis

Table 3. cMRG and EEG findings in epileptic patients with a diagnosis of tuberous sclerosis

No	Cortical tuber Number	location	Subependimal nodule	Astrocytoma	Initial EEG	Follow-up EEG
1	Multiple	Very extensive in the right	+		No EA	No EA
2	Multiple	Extensive	+		Hipsarrhytmia	EA yok, sağ FST, Right F
3	9	biF, right P, bi T	+		Right F	Right F, right T, right FTP
4[a]	Multiple	left F, biT and biO			Right SP	Right SP
5	Multiple	biF, biP, biO	+		Hipsarrhytmia	No EA, biT
6	Multiple	Extensive	+		No EA	No EA, No EA
7[d]	12	biF, biP, right T	+	+	No EA	No EA
8	8	Extensive	+		No EA	No EA
9	Multiple	Extensive	+		No EA	EA yok, EA yok, No EA
10[b]	None		+		No EA	biF
11	9	Extensive	+	+	Hipsarrhytmia	biF
12	12	Extensive	+		Hipsarrhytmia	biT, No EA
13[c]	14	biF, left T, biP	+	+	Extensive	No EA, left FPT, No EA
14[c]	Multiple	biF, biP			Hipsarrhytmia	Right TP, right T
15	12	Extensive	+		Hipsarrhytmia	Sol F
16	Multiple	Extensive, en the largr left O	+		Right TPO	biSP
17	Multiple	biF, biP, right T	+		Left central	biSP
18	2	Left F	+		Hipsarrhytmia	MF
19	6	biF, left P, right O	+	+	Marked MF in the left	Marked biTP, biTO in the left
20	Multiple	biF, biT, biO	+	+	Extensive	No EA, No EA
21	1	Right F			Hipsarrhytmia	biFTO, right FS

[a]right F KD, [b]venous anomaly, [c]White matter involvement positive, F: Frontal; S: Central, P: Parietal; T: Temporal; O: Occipital; KD: Cortical dysplasia, EA: Epileptic Activity; F: Frontal; S: Central, P: Parietal; T: Temporal; O: Occipital; MF: Multifocal

complex affect the quality of life substantially, there is no consensus on the prognosis of seizures yet (15,21). In this study, we investigated the characteristics of epileptic seizures, the prognosis of seizures and the factors which may affect the prognosis of seizures in a group of patients with a diagnosis of epileptic TSC. It has been reported that seizures in tuberous sclerosis complex frequently start in the first year of life and the most common seizure types in this disease include partial seizures and infantile spasm (18,20,21,22). Hence, the most common seizure type in

Table 4. Factors which affect the prognosis of epilepsy in patients with a diagnosis of tuberous sclerosis

	Good prognosis s (%)	Poor prognosis s (%)	*p
Age at the time of the first seizure			0,52
One year and younger (n:16)	7 (43.8)	9 (56.3)	
Above one year of age (n:5)	3 (60)	2 (40)	
First seizure in association with fever (n:7) First seizure without fever (n:14)	3 (42.9) 7 (50)	4 (57.1) 7 (50)	0.76
Histroy of status positive (n:8)	4 (50)	4 (50)	0.864
Histroy of status negative (13)	6 (46.2)	7 (53.8)	
Histroy of infantil spasm positive (n:8) Histroy of infantil spasm negative (n:13)	3 (37.5) 7 (53.8)	5 (62.5) 6 (46.2)	0.466
First antiepileptic drug Vigabatrin (n:7) Other than vigabatrin (14)	 2 (28.6) 8 (57.1)	 5 (71.4) 6 (42.9)	0.22
Location of EA on EEG			0.7
Right	2 (33.3)	4 (66.7)	
Left	2 (50)	2 (50)	
No EA or localized finding	6 (54.5)	5 (45.5)	
First EEG			0.44
Normal	4 (66.7)	2(33.3)	
Focal or extensive EA	3 (50)	3 (50)	
MF or Hipsarrhytmia	3 (33.3)	6 (66.7)	
Number of cortical tubers (s: 20 patients)			0.232
1-6	0 (0)	3 (100)	
7-12	3 (50)	3 (50)	
Multiple	6 (54.5)	5 (45.5)	
Location of tubers (s: 20 patients)			0.426
Extensive bilateral	6 (54.5)	5 (45.5)	
Right	1 (20)	4 (80)	
Left	2 (50)	2 (50)	
Astrocytoma positiver (s:5)	2 (40)	3 (60)	0.696
Astrocytoma negative (s:16)	8 (50)	8 (50)	
Autism /mental or developmental level Autism (-) / normal (s:7)	 4 (57.1)	 6 (42.9)	0.537
Autism (+) or mental retardation-developmental retardation (s:14)	3 (42.9)	8 (57.1)	

*ki kare test; s: hasta sayısı
EA: Epileptik aktivite

our patients was partial seizure and seizures started in the first year of life in 76%. Infantile spasm which has been reported with a rate of 25-69% was found in 38% of our patients (21,23,24,25,26).

In a study in which EEG changes were examined in 361 patients with epileptic TSC, presence of epileptic acitivity on EEG (35% focal, 10% diffuse, 22% hypsarrhythmia) was found with a rate of 78% (27). Although this rate was found to be 76% in our study (focal epileptic activity 66,6%, hypsarrhythmia 38%, diffuse and multifocal epileptic activity 9.5%), focal findings were observed more frequently.

Three types of nodular lesion have been defined in patients with tuberous sclerosis complex: cortical tubers, subcortical heterotopic nodules and subependimal giant cell astrocytoma (28). It has been reported that cortical tubers are observed with a rate of 82-100% (29) and subependimal nodules are observed with a rate of 50-100% (10,30). When the cranial MR imaging findings of our patients were examined, it was found that the frequencies of cortical tuber (95%) and subependimal nodule (85%) were compatible with the literature. Giant cell astrocytoma which is the predominant tumor of tuberous sclerosis complex and has been reported to be observed with a rate of 6-9% (31,32) was observed with a slightly higher rate in our patient group (24%).

Intellectual development is frequently affected in tuberous sclerosis complex and mental retardation has been reported with a rate of 50-55% (20,21,25,33,34). Autism is another neurological disorder which has been reported to be observed with a rate of 30-50% in TSC patients and which affects the quality of life negatively in these patients (35,36). In our study, intellectual and cognitive development levels were found to be below normal in 57% of the patients which was compatible with the literature, whereas autism was found with a lower rate (9.5%). This difference was thought to have arised from the sample size.

It was reported that resistant seizures developed in 65% of the patients and remission occured in 34% (remission: no seizures for at leat one year) at the end of the follow-up period in a study in which 248 patients with epileptic TSC were followed up for 5.5 years (21). In another study, the remission rate for seizures was reported to be 14%, but exacerbation was observed in 25% of these patients in the follow-up (15). At the end of 9 month-10 year-follow-up, it was found that seizures had a good prognosis in 47.6% of our patients and seizures were controlled in 38%. Although interpretation is not possible, since the results may vary according to follow-up times and sample size, we can say that the response to epilepsy treatment in our patients was not very different compared to the literature.

Although the factors which affect the prognosis of seizures were examined by other investigators previously, there is no consensus on this subject. While it was reported that onset of seizures below the age of 1 year in a study and below the age of 6 months in another study might be a risk factor for poor prognosis (8,15), Park ve ark. (37) reported that onset of seizures below the age of one was not related with poor prognosis as also reported in our study. It has been reported that presence of infantile spasm was a risk factor for resistant seizures in some studies (8,21). Although the seizures of our patients who were found to have infantile spasm showed a poorer prognosis, the difference was not statistically significant. This may be explained by the fact that some of our patients who had some partial seizures other than infantile spasm also showed a treatment-resistant seizure prognosis. In addition, it has been reported in the literature that there is no relation between infantile spasm and seizure prognosis (37). Our findings suggest that seizure type and duration in TSC patients alone are not significant in the prognosis in terms of epilepsy.

It has been reported that cognitive functions would have a better prognosis with vigabatrin treatment initiated in the early period by early control of seizures in TSC patients (38). However, we found no effect of initial vigabatrin treatment on the prognosis of seizures in our TSC patients.

In a study conducted in 2003 with a small number of TSC patients, presence of multifocal findings on EEG was reported to be an indicator of poor prognosis (15). This finding was supported by another study which was conducted with 30 TSC patients in 2011 and showed the relation between severe epileptic activity and poor seizure prognosis (8). In the same year, Park et al. (37) reported the presence of a relation between epileptic activity found on the initial EEG and seizure prognosis. When the initial EEG findings of our patients were examined, good seizure prognosis was observed in 67% of the patients with a normal initial EEG and poor seizure prognosis was observed in 67% of the patients who had severe findings including multifocal epileptic activity and hypsarhythmia on the initial EEG. However, no statistically significant relation was found between our initial EEG findings and localization of epileptic activity and seizure activity.

In the literature, the relation between epilepsy and cortical tuber in TSC is one of the subjects which draws much attention (7,8,34,39). It is thought that tubers are epileptogenic, but the molecular basis of epileptogenesis in cortical tubers is not known exactly (40,41). There are different views about cortical tuber and epilepsy prognosis (8,34,37,39). Some investigators have reported that there is a relation between the number of cortical tubers and seizure prognosis, while others have reported that tuber load (tuber/brain ratio) rather than the number of tubers has an effect on seizure control (8,9,39). A different view is that there is no relation between the number of tubers and epilepsy prognosis as concluded in our study (42).

It has been proven that giant cell astrocytoma which is the most common brain tumor observed in TSC is

epileptogenic (7). However, it has been reported that giant cell astrocytoma increases the frequency of seizures in some studies (31). Frequent complex partial seizures continued in 2 of 5 patients in whom we found astrocytoma, while seizures occured as status in one. In two patients, seizures showed a good prognosis. In our study, it was found that presence of astrocytoma on cranial MRI was not a risk factor for seizure prognosis.

Many studies have defended that there is a relation between mental retardation and seizure prognosis (8,21). It has been reported that intellectual and cognitive development retardation are observed in presence of resistant epilepsy in TSC patients. On the other hand, seizures have been reported to show a good prognosis in 82% of TSC patients who have a normal intellectual level (8,21). In our study, good seizure prognosis was found in 57% of our patients who had normal intellectual and cognitive development level and no statisitcally significant relation was found between seizure prognosis and intellectual or cognitive development level.

Although the epileptic seizure characteristics in our patients were not markedly different from the ones reported in the literature, it appears that it is not possible to predict the seizure prognosis according to clinical and laboratory findings. Conclusively, seizure prognosis varies according to different factors for individual TSC patients. Therefore, these patients should be monitored closely considering not only certain criteria, but all factors together. However, large-scale multi-center prospective studies which do not have the limitations of our study are needed to make healthier interpretations.

Acknowledgement

We are thankful to specialist doctor Ş. Senem Başgül (Pediatric Psychiatry), specialist doctor Yusuf Ayhan (pediatric cardiology) and specialist doctors of our opthalmology, dermatology and radiology clinics for their contribution to our study.

Conflict of interest: None declared.

Rerences

1. Osborne JP, Fryer A, Webb D. Epidemiology of tuberous sclerosis. Ann N Y Acad Sci 1991; 615: 125-127.
2. Crino PB, Nathanson KL, Henske EP. The tuberous sclerosis complex. N Engl J Med 2006; 355(13): 1345-1356.
3. Schwartz RA, Fernández G, Kotulska K, Jóźwiak S. Tuberous sclerosis complex: advances in diagnosis, genetics, and management. J Am Acad Dermatol 2007; 57: 189-202.
4. Curatolo P, Bombardieri R, Jozwiak S. Tuberous sclerosis. Lancet 2008; 372: 657-668.
5. Roach ES, Gomez MR, Northrup H. Tuberous sclerosis complex consensus conference: revised clinical diagnostic criteria. J Child Neurol 1998; 13(12): 624-628.
6. Weiner DM, Ewalt DH, Roach ES, Hensle TW. The tuberous sclerosis complex: a comprehensive review. J Am Coll Surg 1998; 187(5): 548-561.
7. Holmes GL, Stafstrom CE; Tuberous Sclerosis Study Group. Tuberous sclerosis complex and epilepsy: recent developments and future challenges. Epilepsia 2007; 48(4): 617-630.
8. Samir H, Ghaffar HA, Nasr M. Seizures and intellectual outcome: clinico-radiological study of 30 Egyptian cases of tuberous sclerosis complex. Eur J Paediatr Neurol 2011; 15(2): 131-137.
9. Goodman M, Lamm SH, Engel A, Shepherd CW, Houser OW, Gomez MR. Cortical tuber count: a biomarker indicating neurologic severity of tuberous sclerosis complex. J Child Neurol 1997; 12(2): 85-90.
10. Roach ES, Williams DP, Laster DW. Magnetic resonance imaging in tuberous sclerosis. Arch Neurol 1987; 44(3): 301-303.
11. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed, text revision [DSM–IV-TR]. Washington, DC: American Psychiatric Association, 2000.
12. Culberton FM, Feral CH, Gabby S. Pattern analysis of Wechsler Intelligence Scale for children-revised profiles of delinquent boys. J Clin Psychol 1989; 45(4): 651-660.
13. Savaşır I, Şahin N. Wechsler çocuklar için zeka ölçeği (WISC-R) el kitabı. Ankara Türk Psikologlar Derneği Yayınları, 1995: 13-52.
14. Anlar B, Yalaz K. Denver II gelişimsel tarama testi Türk çocuklarına uyarlanması ve standardizasyonu el kitabı. Ankara Meteksan Matbası, 1996.
15. Sparagana SP, Delgado MR, Batchelor LL, Roach ES. Seizure remission and antiepileptic drug discontinuation in children with tuberous sclerosis complex. Arch Neurol 2003; 60(9): 1286-1289.
16. Cross JH. Neurocutaneous syndromes and epilepsy-issues in diagnosis and management. Epilepsia 2005; 46(Suppl 10): 17-23.
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(6): 495-499.
18. Józwiak S, Schwartz RA, Janniger CK, Bielicka-Cymerman J. Usefulness of diagnostic criteria of tuberous sclerosis complex in pediatric patients. J Child Neurol 2000; 15(10): 652-659.
19. Webb DW, Fryer AE, Osborne JP. On the incidence of fits and mental retardation in tuberous sclerosis. J Med Genet 1991; 28(6): 395-397.
20. Webb DW, Fryer AE, Osborne JP. Morbidity associated with tuberous sclerosis: a population study. Dev Med Child Neurol 1996; 38(2): 146-155.
21. Chu-Shore CJ, Major P, Camposano S, Muzykewicz D, Thiele EA. The natural history of epilepsy in tuberous sclerosis complex. Epilepsia 2010; 51(7): 1236-1241.
22. Gomez MR. Natural history of cerebral tuberous sclerosis. In: Gomez MR, Sampson JR, Whittemor VH, (eds). Tuberous sclerosis complex: Developmental perspectives in psychiatry. New York: Oxford University Press, 1999: 29-46.
23. Riikonen R, Simell O. Tuberous sclerosis and infantile spasms. Dev Med Child Neurol 1990; 32(3): 203-209.
24. Thiele EA. Managing epilepsy in tuberous sclerosis complex. J Child Neurol 2004; 19(9): 680-686.
25. O'Callaghan FJ, Harris T, Joinson C, Bolton P, Noakes M, Presdee D, Renowden S, Shiell A, Martyn CN, Osborne JP. The relation of infantile spasms, tubers, and intelligence in tuberous sclerosis complex. Arch Dis Child 2004; 89(6): 530-533.
26. Pampiglione G, Moynahan EJ. The tuberous sclerosis syndrome: clinical and EEG studies in 100 children. J Neurol Neurosurg Psychiatry 1976; 39(7): 666-673.
27. Westmoreland B. The electroencephalogram in tuberous sclerosis. In: Gomez MR, Sampson JR, Whittemore VH, (eds). Tuberous sclerosis complex: developmental perspectives in psychiatry. 3th ed. New York: Oxford University Press, 1999: 63-74.

28. Mizuguchi M, Takashima S. Neuropathology of tuberous sclerosis. Brain Dev 2001; 23(7): 508-515.
29. Ridler K, Suckling J, Higgins N, Bolton P, Bullmore E. Standardized whole brain mapping of tubers and subependymal nodules in tuberous sclerosis complex. J Child Neurol 2004; 19(9): 658-665.
30. Baron Y, Barkovich AJ. MR imaging of tuberous sclerosis in neonates and young infants. AJNR Am J Neuroradiol 1999; 20(5): 907-916.
31. Goh S, Butler W, Thiele EA. Subependymal giant cell tumors in tuberous sclerosis complex. Neurology 2004; 63(8): 1457-1461.
32. O'Callaghan FJ, Martyn CN, Renowden S, Noakes M, Presdee D, Osborne JP. Subependymal nodules, giant cell astrocytomas and the tuberous sclerosis complex: a population-based study. Arch Dis Child 2008; 93(9): 751-754.
33. 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(2): 335-344.
34. Kassiri J, Snyder TJ, Bhargava R, Wheatley BM, Sinclair DB. Cortical tubers, cognition, and epilepsy in tuberous sclerosis. Pediatr Neurol 2011; 44(5): 328-332.
35. Smalley SL, Tanguay PE, Smith M, Gutierrez G. Autism and tuberous sclerosis. J Autism Dev Disord 1992; 22(3): 339-355.
36. Wiznitzer M. Autism and tuberous sclerosis. J Child Neurol 2004; 19(9): 675-679.
37. Park SM, Lee YJ, Son YJ, Kim YO, Woo YJ. Clinical progress of epilepsy in children with tuberous sclerosis: prognostic factors for seizure outcome. Chonnam Med J 2011; 47(3): 150-154.
38. Curatolo P, Moavero R. Can we change the course of epilepsy in tuberous sclerosis complex? Epilepsia 2010; 51(7): 1330-1331.
39. Jansen FE, Vincken KL, Algra A, et al. Cognitive impairment in tuberous sclerosis complex is a multifactorial condition. Neurology 2008; 70(12): 916-923.
40. White R, Hua Y, Scheithauer B, Lynch DR, Henske EP, Crino PB. Selective alterations in glutamate and GABA receptor subunit mRNA expression in dysplastic neurons and giant cells of cortical tubers. Ann Neurol 2001; 49(1): 67-78.
41. Wong M, Ess KC, Uhlmann EJ, Jansen LA, Li W, Crino PB, Mennerick S, Yamada KA, Gutmann DH. Impaired glial glutamate transport in a mouse tuberous sclerosis epilepsy model. Ann Neurol 2003; 54(2): 251-256.
42. Doherty C, Goh S, Young PT, Erdag N, Thiele EA. Prognostic significance of tuber count and location in tuberous sclerosis complex. J Child Neurol 2005; 20(10): 837-841.