

Review of Tuberous Sclerosis Complex: A Single Center Experience

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ABSTRACT

Aim: The aim of this study is to review the clinical features and treatment of tuberous sclerosis complex patients followed up in our hospital and to compare our findings with the literature.

Materials and Methods: The clinical-laboratory findings and treatment of 15 tuberous sclerosis patients who presented at a child neurology policlinic between 2007-2017 were retrospectively reviewed.

Results: Fifteen patients aged between 8 months and 17 years were included in the study. The female/male ratio was 47%/53%. Thirteen patients (86%) were referred with convulsions, 1 (7%) with skin hypo-pigmented macule and 1 (7%) with the detection of a renal cyst in ultrasonography. At the time of diagnosis, skin findings were present in 93% of the patients. There were infantile spasms in 23%, focal seizures in 54%, generalized tonic-clonic in 15% and atonic seizures in 8% of those patients who referred with seizures. In addition to the known antiepileptics in treatment, mTOR inhibitors were used in two patients. Forty percent were diagnosed with resistant epilepsy. Seven of the patients (46%) had various levels of mental retardation. There were cardiac findings in 33%, ocular findings in 33%, and renal involvement in 27% of the patients. The most common (87%) neuroradiologic finding was subependymal nodule.

Conclusion: It was observed that the signs and symptoms of our patients were compatible with the literature. In childhood, refractory epilepsy and mental retardation were the most important clinical findings. The age of onset of seizures in patients with resistant epilepsy was under one year of age. These patients had infantile spasms and a larger number of cortical tubers in cranial magnetic resonance imaging findings. It was observed that everolimus treatment had no marked effect on seizure frequency. However, patients with tuberous sclerosis should be closely monitored for the development of malignancies in the long term and this monitoring should be continued in adulthood.

Keywords: Childhood, tuberous sclerosis complex, clinical-laboratory findings-treatments

Introduction

Tuberous sclerosis complex (TSC) is an autosomal dominant inherited genetic disease in which multiple organ involvement is characterized by common hamartomas in many organs especially including the brain, skin, heart, eye, kidney, lung and liver. TSC is due to programmed hyperplasia of ectodermal and mesodermal cells, which is characterized

by epilepsy, adenoma sebaceum and mental retardation. It has a variable age of onset and variable clinical severity. About 2/3 of these cases are formed via spontaneous mutation. Due to mutations in the *TSC1* (9q34) and *TSC2* (16p13.3) genes respectively, the functions of the hamartin and tuberin proteins encoded by these genes are impaired. The mammalian target of hamartin-tuberin proteins is to

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inhibit (mTOR) the signal pathway of rapamycin and thereby control cell growth and proliferation. Clinical findings occur with the impaired inhibitor function of these proteins. Its diagnostic criteria were restructured at the International Tuberous Sclerosis Consensus Conference in 2012. (Table I) (1).

The aim of this study is to review retrospectively the clinical features and treatments of TSC patients who had been referred to our hospital and to compare our findings with the literature.

Materials and Methods

Fifteen patients diagnosed with tuberous sclerosis who presented at the Pediatric Neurology Polyclinic of Aydin Adnan Menderes University Faculty of Medicine between 2007 and 2017 were included in this study. The age, gender, neurological and systemic examinations, the age of onset of convulsions, seizure types, interictal electroencephalography (EEG), cranial magnetic resonance imaging (MRI), abdominal ultrasonography (USG), echocardiography (ECHO) and ocular findings of these patients were evaluated. The seizure classification was carried out according to family testimony, observed seizure activity and classification of the International League Against Epilepsy.

Statistical Analysis

The SPSS 17.0 package program was used in the statistical analyses. Descriptive statistics was utilized, categorical variables were expressed as frequency and percentage. This is a retrospective file scanning study, so informed consent forms were not obtained from the patients. This study was

approved by the Aydin Adnan Menderes University Medical Faculty Ethics Committee (date: 10.05.2018, approval number: 2018/1396).

Results

Fifteen patients (8 male/53%) were included in the study, ranging in age from 8 months to 17 years. The age of the patients at diagnosis was between 2 months and 9 years, consistent with the age at which they were referred to the clinic. Six of the patients (40%) were diagnosed before one year of age, 3 patients (20%) between 1 and 5 years, and 6 patients (40%) at 5 years of age or over. The most common reason for referring to the clinic was convulsion for 13 patients (86%) as well as skin lesions for 1 patient (7%) and renal cyst for 1 patient (7%).

There were skin findings of TSC in 14 patients (93%) at the time of diagnosis. Hypopigmented skin lesions were found in all 14 of these patients, adenoma sebaceum in 5 patients (33%) and unguis fibroma in 2 patients (13%).

Infantile spasms were detected in 3 (23%) of 13 the patients with seizures. The average age of those patients with infantile spasms was 8 months. The first preferred antiepileptic was vigabatrin for those patients with infantile spasms. Seizure control with vigabatrin was achieved in only one patient. There were no seizures in 2 patients treated with ACTH, for 1 month and 7 months respectively. One of these patients was seizure-free for one year with a ketogenic diet, but later focal seizures which were controlled with vigabatrin and topiramate developed. There were 7 patients with focal seizures (54%). Three patients were treated with phenobarbital, 1 patient with vigabatrin, 1 patient with

Major findings	Minor findings
1. Hypomelanotic macule, "ashleaf sign" (≥ 3 , minimum 5 mm diameter)	1. Confetti skin lesions
2. Angiofibromas (≥ 3) or fibrous cephalic plaques	2. Numerous cavities in the tooth enamel (≥ 3)
3. Unguis fibroma (≥ 2)	3. Intraoral fibroma (≥ 2)
4. Shagreen patch	4. Hypopigmentation in the retina
5. Multiple retinal hamartomas	5. Multiple renal cysts
6. Cortical dysplasia	6. Non-renal hamartoma
7. Subependymal nodules	-
8. Cardiac rhabdomyoma	-
9. Subependymal giant cell astrocytoma	*Final diagnosis: 2 major findings or 1 major + ≥ 2 minor finding
10. Lymphangiomyomatosis (LAM)	**Possible diagnosis: 1 major or ≥ 2 minor findings
11. Angiomyolipomas (≥ 2)	A combination of the 2 major features (LAM and angiomyolipomas) without features does not meet criteria for definite diagnosis

carbamazepine, 1 with levetiracetam and 1 patient with valproate as the first antiepileptic treatment. The patient who received carbamazepine treatment was followed up without medication for 1.5 years and the 13-year-old patient who received valproate treatment was followed-up without medication for 10 years. Two patients had generalized tonic-clonic seizure (15%) and one patient had atonic seizure (8%). In 7 patients, seizure control was provided with polytherapy and 5 patients were followed with drug resistant epilepsy. The best response to anti-epileptic treatment in those patients with drug resistant epilepsy

was achieved with vigabatrin and clobazam dual therapy. No response to therapy was observed in the two patients with drug resistant epilepsy who received everolimus (0.1 mg/kg/day max. 10 mg/day) (Table II).

Seven of the patients (46%) had mental retardation. Obsessive compulsive disorder was detected in one patient and two patients had autism.

Rhabdomyoma was detected in 5 (33%) of the patients by ECHO. The earliest age for the diagnosis of rhabdomyoma was 2 months and latest age was 11 years.

Table II. Cranial MRI and EEG findings in tuberous sclerosis patients

No	Age at diagnosis	Number of cortical/subcortical tubers	Subependymal nodule	Other MRI findings	First EEG	Follow-up EEG	AED
1	6 years	2	2	Radial migration line	Centro parietal	Parietotemporal	VGB, LEV
2	3 years	1	-	-	Right frontal	No epileptic activity	-
3	4 years	7	4	-	No epileptic activity	No epileptic activity	CBZ
4	8 month	11	2	-	Focal-generalized	Hypsarrhythmia left parasagittal	PB, VGB, ACTH, CBL
5	10 months	9	2	-	Right parasagittal	Generalized	VGB, LEV, CBL
6	2 months	5	2	-	No epileptic activity	Bilateral temporal	VGB, VPA, CBL
7	5 years	14	6	Cerebral atrophy, SEGA	Left temporal	Bilateral frontal-centrotemporal	VGB, LEV, CBZ, TPM, CBL, VPA, LCS, ZNS, EVL
8	9 months	9	4	-	Hypsarrhythmia	Left parietal	VGB, ACTH, KETOGENIC DIET, TPM
9	6 years	5	3	-	Right frontal	No epileptic activity	-
10	5 years	7	4	-	Right parietooccipital	No epileptic activity	VPA, OXCZBZ, CBL
11	2 months	9	2	-	Hypsarrhythmia	Right parieto occipital	PB, VGB, CBL
12	5 years	13	2	Venous angioma	Generalized	Right frontal	VPA, OXCZBZ, LEV, CBL
13	5 months	7	3	Thin corpus callosum	Hypsarrhythmia	Left temporoparietal	VGB, ACTH, CBL
14	5 years	6	1	Cerebral atrophy	Left parietooccipital	Fokal-generalized	LEV, VPA, CBL
15	2 years	14	-	-	Right frontal	Hypsarrhythmia right frontal	LEV, VGB, VPA, CBL, TPM, CLN, RFM, EVL

MRI: Magnetic resonance imaging, EEG: Electroencephalography, SEGA: Subependymal giant cell astrocytoma, AED: antiepileptic drug, CBZ: Carbamazepine, VGB: Vigabatrin, LEV: Levetiracetam, PB: Fenobarbital, ACTH: Adrenocorticotrophic hormone, CBL: Clobazam, VPA: Valproic acid, TPM: Topiramate, OXCZBZ: Okskarbazepin, EVL: Everolimus, RFM: Rufinamide, CLN: Clonazepam

Findings of ocular involvement of TSC were detected in 5 of the patients (33%). Two of them (13%) had retinal hamartoma, one had retinoblastoma, astrocytoma and a hypo-pigmented area in the retina.

In the renal USG, Angiomyolipomas was determined in 4 (27%) patients and two of them were bilateral.

Cortical/subcortical tubers and/or subependymal nodules were detected in all patients. The most common finding in cranial MRI was subependymal nodules (87%). Subependymal giant cell astrocytoma (SEGA) developed in one of the cases (Table II).

Discussion

TSC, which affects many systems including the brain, skin, kidney, eye and heart, was first described by Bourneville in 1880 (2,3). Its incidence is estimated to be 1 in 5.800 (4). The most common neurological complication is convulsion, which occurs in about 90% of patients and begins in the first year of life in 1/3 of patients (5,6). Consistent with the literature, epilepsy was present in 87% of our cases and seizures started in the first year of life in 46%. Infantile spasms, which are seen in 30-60% of TSC, were the first referral cause in 23% of our cases (6-8).

Skin manifestations are common in TSC. The most common skin findings are hypopigmented macules. Usually lesions are seen from birth, while they become more apparent in the first years of life (9,10). Adenoma sebaceum is usually observed in the adolescence period (8,11,12). Hypopigmented skin lesions were present in 93% of our patients and adenoma sebaceum in 33%, skin lesions were not detected in only one 8-year-old patient.

The most common cardiac finding in TSC is rhabdomyoma, one of the tumours with a good prognosis found in 60-80% of cases (13-15). Cardiac rhabdomyomas are detected during the antenatal period or infancy and then stabilization or spontaneous regression is observed with age. The development of a new cardiac rhabdomyoma after infancy is very rare. In one study, a patient at the age of 2 years with rhabdomyoma was presented requiring a new resection after a rhabdomyoma resection as a new-born (16). Rhabdomyomas are usually asymptomatic but may cause atrial or ventricular arrhythmias, sinus node dysfunction and heart block. Even if these cases are asymptomatic, it is necessary to observe new rhabdomyomas and cardiac conduction defects that may develop in follow-up (17,18). There was rhabdomyoma in 33% (5 patients) of the patients in our study. Regression was observed in 3 patients and there was no change in size in 2 patients.

The most common renal lesions are Angiomyolipomas and renal cysts. Renal angiomyolipomas occur in about 50% of the patients (19). While the frequency of angiomyolipomas increases with age, there is no such relationship in renal cysts (20). Renal involvement was detected in 27% of our patients, lower than the rate reported in the literature. This was related to the young age of our patients.

Ocular findings of patients with TSC include retinal and non-retinal lesions. Retinal hamartomas remain stable for many years and rarely affect vision. Non-retinal lesions consist of depigmentation in the iris, choroid coloboma, and eyelid angiofibromas. Eye findings were reported at different rates in the literature. Retinal hamartoma was found in 44%, 10.2% and 25% in different studies (21,12,22). In a cohort study in the United States, they were seen in approximately 50% of patients (23). There were findings of ocular involvement in 33% of our patients.

Cranial lesions in TSC are developmental anomalies such as cortical tubers, subependymal nodules, heterotopic grey and white matter abnormalities, and SEGA. It has been reported that cortical tubers are seen at a rate of 82-100%, and subependymal nodules at a rate of 50-100% (7,24). When the cranial MRI findings of our cases were examined, the incidence of the cortical tuber (93%) and subependymal nodule (86%) was consistent with the literature. Giant cell astrocytomas are seen in 10-15% of patients with TSC and frequently in the first 20 years. In one study, the mean age of diagnosis of SEGA was 13.3 years (25). Therefore, yearly MRI scans up to 21 years of age are recommended (25-27). In one of our patients, SEGA was detected at the age of 11 years.

In TSC, mental retardation is reported at a rate of about 50% (5,28). There was a significant relationship between the average number of cortical tubers of more than 7-10, the presence of these tubers in the occipital lobe, the presence of infantile spasm in the history and the learning disability (29,30). Various levels of mental retardation were detected in 46% of our patients. The cortical tuber number was between 9 and 14 in cranial MRI in our patients with infantile spasm and learning disability. These cortical tubers were mostly located in the occipital region. The cortical tuber numbers in patients without learning disabilities were between 1 and 5.

The association of autism with TSC has been reported at a rate of 25-50% (31,32). Early-onset of seizures is also associated with severe cognitive impairment and autism-like behavior (6,33). In our cases, obsessive compulsive disorder was detected in one patient and two patients had autism. The fact that it was detected less than the literature

may be associated with the low number of patients in our study.

Epilepsy is the most common neurological finding in patients with TSC (6). The most common types of seizures are infantile spasm or focal seizures, but most of them also have other types of seizures, such as tonic, clonic, tonic-clonic, myoclonic, atonic, and atypical absences (34). Infantile spasms can also turn into epileptic spasms (6,35). Focal seizures were mostly commonly observed in our patients (40%). The earliest seizure onset age was 1 month and the average age was 16 months. The presence of epileptic activity in EEG was found to be 76% (28.5% focal, 9.5% generalized, 38% hypsarrhythmia) in one study (7). Epileptic activity was detected in 80% of our patients (47% focal, 13% generalized, 20% hypsarrhythmia). The presence of early onset seizures in children with TSC increases the risk of developing resistant epilepsy and/or epileptic encephalopathy. It was shown that 42% of children who were diagnosed with TSC before the age of 2 years developed drug resistant seizures (6). In a meta-analysis, vigabatrin was found to be effective in 95% of cases with infantile spasms (36). However, visual field defects (incidence 30-40%) limits the usage of the drug (37,38). Valproate and topiramate have similar efficacy for infantile spasm. Vigabatrin can be used as a single agent in infantile spasm and add-on therapy can be applied when drug resistance develops (38,39). Benzodiazepines such as nitrazepam and clonazepam are rarely efficient as a single agent for infantile spasm and are often used as adjunctive therapy or rescue medication. Antiepileptic drugs such as topiramate, lamotrigine, levetiracetam, zonisamide, and carbamazepine were found effective in preventing seizures or reducing seizure frequency in other seizure types in TSC (40,41). Felbamate is a useful for individuals with partial-onset refractory partial seizures, especially together with vigabatrin (42). It has also been shown that clobazam is a potential beneficial agent in TSC (43). More than 20% of patients with TSC can develop drug resistance epilepsy. For these patients, ketogenic diets, vagal nerve stimulation and resective epilepsy surgery are increasingly used (44). An over 50% reduction in seizures was observed in 11 of 12 refractory epilepsy patients who received ketogenic diet (45). In a study on epilepsy surgery, 37 out of 70 patients (53%) were seizure free and a further 8 (11%) had a significant decrease in seizure frequency (46).

In our patients, the best response to anti-epileptic treatment in patients with resistant epilepsy were achieved with vigabatrin and clobazam dual therapy. At a rate of 40%, seizures resistant to treatment continue. The age

of onset of seizures in patients with resistant epilepsy is under 1 year of age and prevalent for those who have a large number of cortical tubers in their cranial MRI findings. Increasing evidence suggested that mTOR inhibitors may be useful in the treatment of epilepsy in TSC. mTOR is a serine/threonine kinase belonging to the phosphatidylinositol 3-kinase (PI3K)-related protein kinase family. It plays an important role in the regulation of a number of cellular functions, including particularly cell growth, metabolism and proliferation and in the maintenance of cellular homeostasis. Glutamate, an excitatory neurotransmitter and subclinical epileptiform discharges increase mTOR activity. mTOR regulates long-term synaptic potency, depression and epileptogenesis learning and memory formation (47,48).

Many investigators have found an improvement in learning disability, seizure frequency, survival and motor development for TSC-related mice, following treatment with everolimus or rapamycin (mTOR inhibitors) (47,49). In non-TSC animal models, rapamycin inhibits epileptogenesis in post-traumatic epilepsy (50). Significant reduction in seizure frequency was observed in treatment with rapamycin in patients with TSC (51). In one study, 5 out of 7 patients with resistant epilepsy treated with rapamycin were seizure-free after 6 months of treatment (52). In a multicentre study, everolimus as an adjunctive therapy for treatment-resistant focal onset seizures was compared with a placebo. A significant decrease in seizure frequency was found (53). Another randomized controlled study showed that sirolimus treatment resulted in a 41% reduction in seizure frequency (54). In our study, two refractory epilepsy patients received everolimus but no marked change in seizure frequency was achieved.

Study Limitations

This study has small number of patients with TSC and the lack of a longer follow-up term, including into adulthood are considered to be the limitations of our study.

Conclusion

We found that the clinical features, organ involvement, and treatment resistance of our patients were not different from the literature. The onset age of seizures in patients with resistant epilepsy was under 1 year of age and they had a larger number of cortical tubers in their cranial MRI findings. Patients with tuberous sclerosis should be closely monitored for the development of malignancies due to defective tumor suppressor genes. The need for this observation should be continued in adulthood

especially in terms of giant cell astrocytoma in patients with subependymal nodules, cardiac conduction defects in patients with rhabdomyoma, and for the development of "lymphangioliomyomatosis" in women.

Ethics

Ethics Committee Approval: This study was approved by the Aydın Adnan Menderes University Faculty of Medicine Ethics Committee (date: 10.05.2018, approval number: 2018/1396).

Informed Consent: This is a retrospective file scanning study, so informed consent forms were not obtained from the patients.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: A.T., A.A., Design: A.T., Data Collection or Processing: B.K.Y., Supervision: A.A., Writing: A.T., B.K.Y.

Conflict of Interest: No conflict of interest was declared by the authors.

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