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Olgu Sunumu | Case Report

EVEROLIMUS TREATMENT IN REFRACTORY EPILEPSY DUE TO TUBEROUS SCLEROSIS COMPLEX: A SINGLE -CENTER CASE SERIES

TUBEROSKLEROZ KOMPLEKSİNE BAĞLI DİRENÇLİ EPİLEPSİDE EVEROLİMUS TEDAVİSİ: TEK MERKEZ OLGU SERİSİ

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ABSTRACT

Feokromasitoma sempatik sinir sisteminin kromaffin hücrelerinden gelişen Tuberous sclerosis complex is an autosomal dominant-inherited multisystem neurocutaneous genetic disorder manifesting hamartomas and skin lesions involving all systems of the body. The inactivation of the inhibition in the mTOR pathway due to mutations in *TSC1* and *TSC2* causes the clinical and pathological manifestations of this disease. Epilepsy is the most common clinical feature in the course of the disease and is generally resistant to conventional antiepileptics. Everolimus is an mTOR inhibitory agent formerly used in the treatment of hamartoma and used in resistant epilepsy owing to the tuberous sclerosis complex with its disease-modifying effect. In recent years, everolimus has been used increasingly in the treatment of resistant epilepsy due to tuberous sclerosis complex. In this study, we retrospectively evaluated the response of 3 patients suffering from tuberous sclerosis and resistant epilepsy treated with everolimus.

Keywords: Tuberous sclerosis complex, epilepsy, everolimus, mTOR inhibitors.

ÖZ

Tüberoskleroz kompleksi, vücudun tüm sistemlerinde görülebilen hamartomlar ve deri lezyonları ile kendini gösteren, otozomal dominant geçişli, multisistemik bir nörokutanöz hastalıktır. TSC1 ve TSC2 genlerindeki mutasyonlar nedeniyle mTOR yolağının inhibisyonun inaktivasyonu, hastalığın klinik ve patolojik bulgularına neden olmaktadır. Epilepsi, tüberoskleroz kompleksi seyrinde en sık görülen klinik bulgudur ve genellikle konvansiyonel antiepileptiklere dirençli nöbetler ile seyretmektedir. Everolimus, daha önce tüberoskleroz kompleksindeki hamartomların ve nöbetlerin tedavisinde kullanılan hastalık modifiye edici etkisi olan bir mTOR inhibitör ajanıdır ve son yıllarda tüberoskleroz kompleksine bağlı dirençli epilepsi tedavisinde giderek artan bir şekilde kullanılmaktadır. Bu çalışmada, kliniğimizde tüberoskleroz kompleksi ve dirençli epilepsi tanıları ile izlenen ve everolimus tedavisi verdiğimiz 3 hastanın tedavi yanıtını ve klinik bulgularını değerlendirdik.

Anahtar Kelimeler: Tüberoskleroz kompleks, epilepsi, everolimus, mTOR .

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Introduction

Tuberous sclerosis complex (TSC) is an autosomal dominant disorder, inherited and multisystem neurocutaneous, with an occurrence rate of 1 per 6,000 to 10,000 live births.[1] TSC classically involves the brain, skin, kidneys, heart, eyes, and lungs, but can affect any system. However, the hallmark of the disease is tumors consisting of glial-neuronal and retinal hamartomas, subependymal giant cell tumors (SEGA), cardiac rhabdomyomas, renal and extra-renal angiomyolipoma's (AML), and pulmonary lymphangioleiomyomatosis (LAM).[2] Mutations in either *TSC1* or *TSC2* lead to TSC. *TSC1* and *TSC2* are located on chromosome 9q34, and chromosome 16p13 respectively, where *TSC1* encodes hamartin and *TSC2* encodes tuberin proteins. [2,3] Hamartin and tuberin are widely expressed throughout the normal tissues; together, these proteins are involved in the mammalian target of the rapamycin (mTOR) pathway. This pathway functions to regulate cell growth, size, and proliferation. Deregulation of the mTOR signaling pathway can result in tissue overgrowth as the TSC2:TSC1 complex stops the mTOR activation.[2,4] Overactivation of mTOR leads to a giant, dysplastic neurons, abnormal axonogenesis, dendrite formation, increased excitatory synaptic currents, reduced myelination, and disruption of the cortical laminar structure, resulting in hamartomas, neuropsychiatric disorders, and epilepsy associated with TSC.[5]

Epilepsy is the most common neurological symptom in TSC. Although epileptic seizures are observable at any stage of the disease, two-thirds of them start in early infancy.[5,6] Although all types of seizures can be seen, 10–25% of all patients have rapid, symmetrical, clustered flexion, or extension spasms of the extremities or neck.[2,6] Vigabatrin is the drug of the first choice for the treatment of infantile spasms associated with TSC. In unresponsive cases, conventional antiepileptics such as adrenocorticosteroids (ACTH), ketogenic diet, vagal nerve stimulation (VNS), or epileptic surgery treatments may reduce the seizure frequency.[2,6] Unfortunately, >60% of all patients are resistant to these therapies.[5] Autism spectrum disorder (ASD), attention deficit and hyperactivity disorder (ADHD), and intellectual disability are neuropsychiatric disorders that have been reported in 90% of all patients and are called TSC-related neuropsychiatric disorders (TAND).[7]

Everolimus is an mTOR inhibitor that has been approved for the treatment of subependymal giant cell astrocytoma and renal angiomyolipoma in patients with TSC.[8-10] It was first used to treat hamartomas, anjiofibromas, and SEGAs in TSC.[8] It has been approved for use in the treatment of renal AMLs and intractable epilepsy in TSC based on the results of subsequent studies.[5,10,11] We evaluated the responses to everolimus treatments of 3 patients who long-term followed up with diagnosis of TSC, and had resistant seizures despite two or more conventional antiepileptic treatments, and varying degrees of cognitive and mental developmental retardation. Before the treatment, the parents of the patients were informed about the everolimus treatment and its possible side effects, verbal and written consents were obtained from the parents.

Cases

Case1

The first case was a 16-year-old girl diagnosed with TSC and resistant epilepsy since her infancy, along with heart rhabdomyoma and renal AMLs. On physical examination, she had a large angiofibroma on her face, multiple hypopigmented macules on her body, mostly on the trunk, and ash leaf sign on her sacral area. Her school success was low and had low borderline intelligence (WISC-R 80). Imaging findings showed cortical tubes (Figure 1), cardiac rhabdomyoma and bilateral renal AMLs Genetic examination revealed p.Arg147Serfs*49 heterozygous mutation in TSC2 gene. At the start of the therapy, she was taking vigabatrin (1gr/day), levetiracetam (2gr/day), and sodium valproate (2gr/day). Other than these, there was no known history of antiepileptic use. Despite medication, she continued to have seizures of varying severity, most of which were generalized tonic and gelastic seizures which episodes of inappropriate laughing and crying. Everolimus treatment was started to the patient at a dose of 10 mg/day. In the first and sixth months of therapy, seizure frequency was reduced by more than 50%. Gelastic seizures disappeared completely and a significant shortening was observed in the duration of the other seizures. No clinical or laboratory adverse effects were observed during treatment.

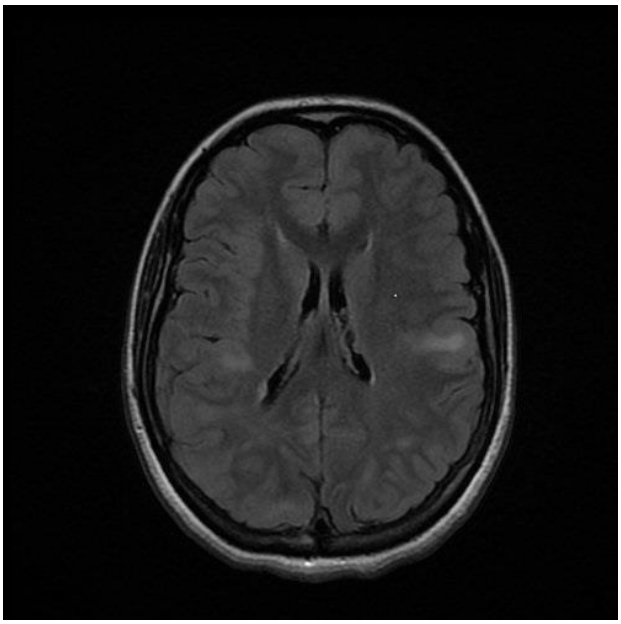

Figure 1. Bilateral cortical tubers on T1-weighted imaging

However, no significant changes were observed in the dimensions of cerebral tubers, cardiac rhabdomyoma and renal AMLs in the results of cranial magnetic resonance imaging (MRI) and renal ultrasonography (USG) imaging evaluated at the 6th month of treatment.

As a result of the positive treatment response, sodium valproate treatment was tapered and discontinued.

Case 2

The second case was an 11 year old male diagnosed with AMLs and cortical tubers in antenatal follow-up. He was followed up with the suspicion of metabolic disease in the neonatal period and was diagnosed with congenital adrenal hyperplasia. On physical examination, there are hypopigmented macules on the face and trunk. The patient had a normal motor neurologic examination but had a moderate mental retardation (WISC-R 55). Imaging findings showed cortical tubers (Figure 2) and bilateral renal AMLs. Genetic examination revealed c.1832G>A heterozigot heterozygous mutation in TSC2 gene. There were previous history of using different combinations of vigabatrin, sodium valproate, levetiracetam, and topiramate. Despite these antiepileptic treatments, he had a history of intensive care admissions with the diagnosis of status epilepticus twice. At the start of his therapy, he was taking levetiracetam (40mg/kg/day), sodium valproate (40mg/kg/day), and topiramate (5mg/kg/day). After initiation of 10mg/day everolimus treatment the patient's seizure frequency reduced by more than 50% in the first month of therapy, and he was seizure-free in 6th month. No clinical or laboratory advers effects were observed during treatment. But similar to the first case no significant changes were observed in the dimensions of cerebral tubers, and renal AMLs in the results of cranial MR and USG imaging evaluated at the 6th month of treatment.

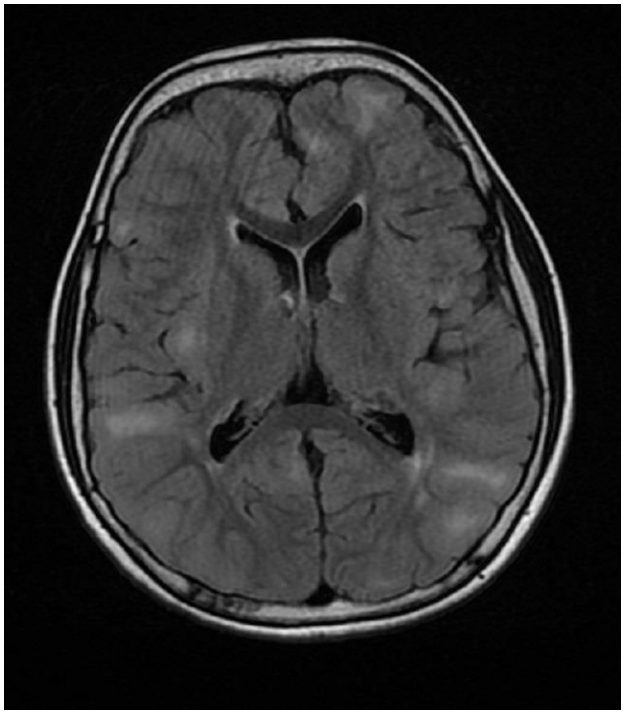

Figure 2. Bilateral diffuse cortical tubers on T1 weighted imaging

Case 3

Third case is a 6-year-old girl was followed up with the diagnosis of TSC, renal AML, ASD, and resistant epilepsy. She was diagnosed with cardiac rhabdomyoma in the antenatal period and had persistent spasms and generalized tonic seizures since the neonatal period. On physical examination, there are scarce hypopigmented macules on her body, and was followed up with the diagnosis of ASD. Imaging findings showed cortical tubers (Figure 3), cardiac rhabdomyoma and bilateral renal AMLs. Genetic examination revealed p.H1746.R1751del heterozygous mutation in TSC2 gene. Her antiepileptic treatment were levetiracetam (40mg/kg/day), and sodium valproate (30mg/kg/day) at the beginning of everolimus treatment. Severe stomatitis and related nutrition difficulties developed in the first week after everolimus 5mg/day treatment was started. Despite interrupting treatment for 2 weeks and initiation of treatment with dose titration (2.5mg/day) stomatitis repeated and her oral nutrition deteriorated therefore patient's everolimus treatment discontinued. The demographic and clinical findings of the case patients are summarized in Table 1.

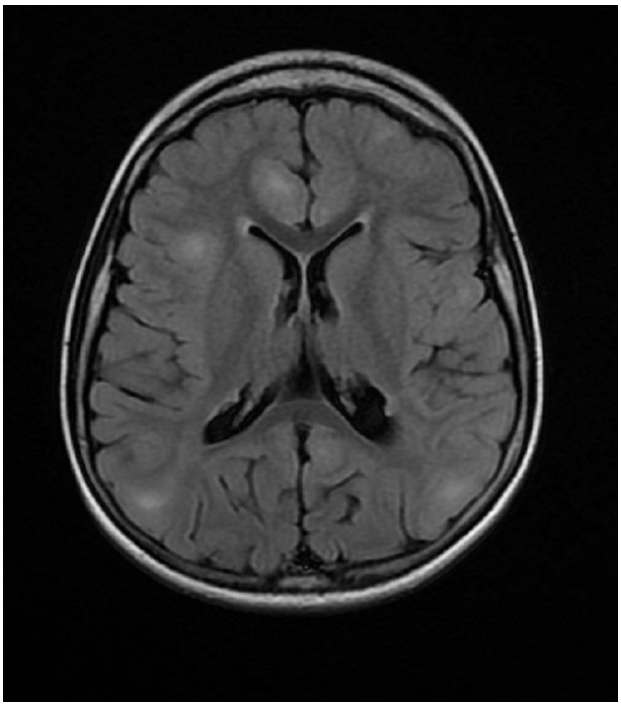

Figure 3. Bilateral diffuse cortical tubers on T1 weighted imaging

Discussion

There is still no consensus on the optimal treatment of epilepsy in individuals with TSC. Antiepileptics used in the treatment of TSC are usually effects by the regulation of gamma-aminobutyric acid (GABA), glutamate, or ion channels without any disease-modifying effects. After demonstrating the role of uncontrolled activation of the m-TOR pathway in the pathogenesis of TSC, m-TOR

inhibitors have been increasingly used to treat components of the disease. In the EXIST-1 multicenter controlled double-blind study, first published in 2013, everolimus treatment was reported to reduce >50% the size of subependymal giant cell tumors in TSC. In conclusion, everolimus may be considered in disease-modifying therapy for the treatment of other components of TSC.[11] In a subsequent study conducted on 118 adult patients (EXIST-2), a significant reduction was detected in the size of angiomyolipoma after everolimus treatment.[10] The first prospective study of everolimus therapy in the treatment of epilepsy in TSC was conducted by Krueger et al.[9] A significant decrease ($p < 0.0001$) in seizure frequency was recorded at the end of the 4th and 12th week of the start of everolimus treatment in pediatric and adult TSC patients, and the response to treatment was found to be dose-dependent.

Table 1. Demographic and clinical features of patients

	Case 1	**Case 2**	**Case 3**
Gender	Female	Male	Female
Age	16	11	6
Gen mutation	TSC2 p.Arg147Serfs*49 heterozygous	TSC2 c.1832G>A heterozygous	TSC2 p.H1746.R1751del heterozygous
Cardiac RM	+	-	+
Renal AML	+	+	+
Concomitant disorders	Mild MR	KAH + moderate MR	ASD
Concomitant AE's	LEV, VPA, VGB	LEV, VPA, TPA	LEV, VPA
Everolimus dosage	10mg/day	10mg/day	5mg/day,(subsequently 2.5mg/day)
Response to treatment (1th Month)	>%50 seizure frequency decrease	>%50 seizure frequency decrease	N/A
Response To Treatment (6th Month)	>%50 seizure frequency decrease + absence of gelastic seizures	Seizure free	N/A
Adverse effects	None	None	Severe stomatitis

LEV: Levetiracetam, Valproic acid, TPA: Topiramate, VGB: Vigabatrin, MR**:** Mental Retardation

A higher rate of seizure control was achieved at the dose of 10 mg/day compared to that at the dose of 5 mg/day. In this study, one of the 3 patients was completely seizure-free, while the other had a >50% decrease in seizure frequency and shortened seizure durations. In our patient who had OSD together with TSC, because of the side effects, the medicine was not administered at the optimal dose and duration; therefore, the effect of seizure frequency could not be assessed.

Along with epilepsy, cognitive disorders such as learning difficulties, ADHD, and OSD often accompany TSC.[12] Neurobiochemical processes induced by epilepsy or antiepileptic drug side effects appear to play a role in the formation of this process. There may also be psychiatric problems caused by the psychology of chronic illness. However, mTOR hyperactivation has been implicated not only in cell proliferation and epileptogenesis but also in the etiology of neuropsychiatric pathologies.[13] There are no prospective studies, however, on everolimus therapy of neurocognitive function in TSC patients. However, no statistical improvement in the quality of life scales of patients with TSC and SEGA was observed in a study with everolimus treatment in patients with TSC and SEGA[8], but a significant increase in the quality of life scale was observed in a study with sirolimus, another mTOR inhibitor, in patients with TSC and renal AMLs.[14] While a significant improvement was observed in the psychiatric evaluation and quality of life scale of the adolescent girl in our study, there was no improvement in ADHD and mental developmental delay in the patient followed up with the diagnoses of CAD and TSC. Because the medicine could not be used promptly, the patient we followed up with ASD was not examined.

No significant changes were observed in echocardiography, cranial MR, and abdominal USG imaging of our patients at the 6th month. Studies with the effect of mTOR inhibitors on hamartoma sizes in TSC were of longer duration.[10,11] We, therefore, believe that this result can be attributed to the fact that we could not reach sufficient treatment time for a reduction in mass sizes in our patients.

Around 15% of people have negative side effects. The most prevalent adverse effects during therapy include upper respiratory tract infection and stomatitis. Other typical adverse effects include diarrhea, fever, anorexia, and rash, which may easily be managed with the medication dosage titration.[9] Pneumonia, worsening seizures, and status epilepticus are all serious side effects. Although the specific cause of these adverse effects is unknown, it has been reported that they are more prevalent in children under the age of 6 years and that fatalities due to sudden unexpected death in epilepsy (SUDEP) and pneumonia have occurred during therapy.[9,15,16]

In recent studies and reviews, in which the efficacy and side effects of everolimus treatment were evaluated, similarly in our cases, decrease in seizure frequency and the number of seizure-free days was observed after everolimus treatment, while the adverse effect profile increased as the age range decreased, especially under the age of 3.[17,18] Although there is no consensus for the appropriate dose for the age range, it is stated that serum

levels in the range of 5-15 ng/mL are appropriate in terms of treatment efficacy and safety of adverse effects.[17-20] It is thought that early treatment with everolimus can prevent seizures and cognitive decline and neuropsychiatric comorbidities due to TSC complex.[17] Experimental studies for new mTOR pathway modifier agents such as cannabidiol are ongoing for their effects and adverse effects.[18]

Since everolimus was provided with special permission for TSC patients and considering that the treatment is costly, the number of our patients was restricted, and whereat we do not have possibility, for not to follow serum everolimus levels during the treatment process. which forms a limitation of our research.

In conclusion, TSC associated refractor seizures depends on the pathology in the mTOR pathway. Everolimus appears to be an effective and safe treatment option with its disease-modifying mechanism of action in the treatment of resistant seizures in TSC. Other favorable benefits include a decrease in the size of hamartomas and an increase in neurocognitive function. We thus believe that long-term studies should be conducted with large patient groups to evaluate the long-term side effects.

Compliance with Ethical Standards

Verbal and written consent was obtained from the legal parents and guardians of the subjects.

Conflict of Interest

There is no conflict of interest between the authors.

Author Contribution

Authors contributed equally to this work.

Financial Disclosure

The authors declare no financial support.

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