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Adjunctive Everolimus Therapy in Tuberous Sclerosis-Associated Refractory Epilepsy

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Abstract

Presentation

In this article we are reporting the beneficial impact of everolimus treatment on the renal & CNS manifestations of TSC.

Diagnosis

The patient diagnosed with refractory seizure associated with tuberous sclerosis.

Treatment

The patient was treated with everolimus, and he was commenced at a dose of 10 mg daily.

Conclusion

This report shows that everolimus treatment for three years of refractory seizures in patients with TSC, can lead to a clinically meaningful reduction in seizure frequency. Compared with other anti-epileptic medications, everolimus demonstrated additional benefits in reducing Subependymal giant cell astrocytoma (SEGA) and renal angiomyolipoma volume. At the time of preparation of this report, the patient continue treatment with daily everolimus without adverse events.

Introduction

Tuberous sclerosis complex (TSC) is a multisystem autosomal dominant uncommon genetic disorder that affects many organ systems.TSC patients most often present with neurologic symptoms, with approximately ninety percent (90%)of affected individuals experiencing seizures.[1]

There have been a number of recent studies describing the long-term use of everolimus (mTOR inhibitor) for management of refractory seizure and renal angiomyolipoma associated with tuberous sclerosis.[2]

Many seizure types can be seen in individuals with tuberous sclerosis, including tonic, tonic-clonic, myoclonic, and atypical absence.[3] The seizures are often refractory to the medical therapies.[4] Renal manifestations are the second most common findings associated with TSC, with angiomyolipomas occurring in eighty percent (80%).[5]

TSC is caused by mutations in the TSC1 and/or TSC2 genes which regulate mTOR, a key molecular control in cell proliferation and differentiation. Thus, mutations at the *TSC1* and *TSC2* loci may result in loss of control of cell growth and cell division, and therefore a predisposition to tumour formation.[6]

In recent years, mTOR inhibitors have been approved by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) for treatment of Subependymal giant cell astrocytoma (SEGA), renal angiomyolipomata, and lymphangioleiomyomatosis (LAM) in patients with TSC.[7]

Here we report the beneficial impact of everolimus treatment on the manifestations of TSC in a thirty 31-year-old patient with refractory epilepsy.

Case report

In June 2003, a male patient was referred to the epilepsy service in Beaumont Hospital for management of intractable generalized epilepsy associated with TSC. He had initially presented with infantile spasms at three months of age. Over the years, he has been treated with different regimes of standard antiepileptic drugs (AEDs).

His seizure pattern included clusters of two to three seizures daily, consisting of tonic posturing, tonic falls, and generalized tonic-clonic seizures. His Renal screening with ultrasound and CT revealed multiple angiomyolipomata (AML) in both kidneys. Initial MRI brain showed multiple cortical tubers, and multiple subependymal nodules.

The patient had been evaluated in the epilepsy monitoring unit (EMU) and findings were consistent with multifocal onset of seizures. Despite extensive multiple combinations of different AEDs, the patient remained refractory. Based on his video EEG findings, it was determined that focal resection was not an option. In view of his systemic involvement, treatment-refractory seizures and following a discussion with his family, it was decided that he might benefit from treatment with everolimus, and this was commenced at a dose of 10 mg daily.

At three years of follow-up, the patient is maintained on everolimus, with excellent tolerability. There has been a significant improvement in the number of disabling seizures. His parents report no admissions to hospital, his need for rescue benzodiazepine therapy has decreased. Follow up renal imaging has showed reduction in the size of renal tumors (Figure 1). There has also been a reduction in subependymal nodules.

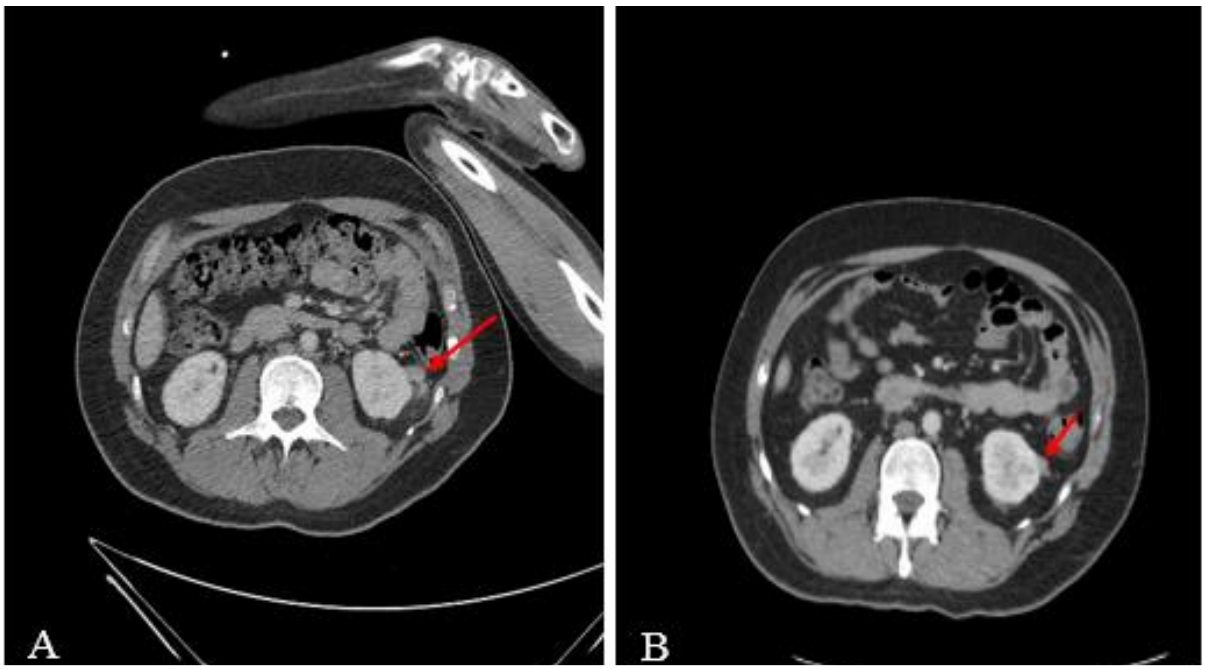

Figure 1: Renal CT performed in 2014 (pre-treatment) shows an angiomyolipoma measuring 2.2 cm arising from the lower pole of the left kidney (A). Follow up renal CT (36 months post treatment) shows a decrease in size of the same lesion to 1.2 cm (B).

Discussion

Tuberous sclerosis complex is an autosomal dominant genetic disorder with an incidence of approximately 1 in 5000 to 10,000 live births. It is caused by a mutation in either the TSC1 or the TSC2 gene.[8] TSC1 gene encodes the protein, hamartin, which is widely expressed in normal tissues. Hamartin forms a complex with the tuberin protein which is encoded by the TSC2 gene. Hamartin and tuberin are involved in the control of cell growth and cell division through inhibition of cellular signalling mediated by the mechanistic target of rapamycin (mTOR). Understanding the role of hamartin-tuberin complex in mTOR signalling has led to the development of the mTOR inhibitor everolimus, a novel precision therapy for patients with TSC.

Several clinical studies have reported the benefits of oral everolimus in reducing SEGA and renal angiomyolipoma volume. The EXIST-3 trial was a prospective, randomised, multicentre, double-blind, placebo-controlled, phase 3 study evaluated the efficacy and safety of two dosing regimens of adjunctive everolimus compared with placebo in patients with tuberous sclerosis complex and treatment-resistant focal epilepsy.[9] The findings from EXIST-3 provide evidence that everolimus is an effective treatment option as adjuvant therapy for children and adults with treatment-resistant epilepsy.

In conclusion, this case report shows that everolimus treatment of mixed-type seizures in patients with TSC, despite the high baseline burden of seizures, can lead to a clinically meaningful reduction in seizure frequency. Reports suggesting that long term use of everolimus with median treatment of nearly three years have not revealed any additional safety concerns.

Declaration of Conflicts of Interest:
The authors have no conflicts of interest to declare.

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