Research Square

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Everolimus therapy in a patient with tuberous sclerosis and a mutation in the LRP5 gene

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Abstract

Tuberous sclerosis complex (TSC) is an autosomal dominant disorder characterized by hamartomatous lesions affecting multiple organs. Renal involvement is major cause of morbidity and mortality, with angiomyolipomas being the most common manifestation, whereas renal cystic disease is less frequently. We present a patient diagnosed with TSC with bilateral renal enlargement and multiple renal cysts. Genetic testing revealed no pathogenic variants in TSC1 and TSC2, but identified a heterozygous LRP5 variant. Everolimus was initiated at 4 years of age. During 3.5 years of follow-up, progressive renal enlargement and cystic disease were observed despite preserved renal function. No previous case of TSC with an LRP5 variant has been reported. The potential role of this variant in the renal phenotype and response to everolimus remains unclear.

Summary

What is new: First reported case of TSC with an LRP5 variant and progressive cystic kidney disease despite everolimus therapy, suggesting a potential genetic modifier.

Introduction

Tuberous sclerosis complex (TSC) is an autosomal dominant hereditary disorder caused by pathogenic variants in the TSC1 or the TSC2 genes, encoding hamartin and tuberin. Dysregulation of the mTOR pathway leads to abnormal cellular growth and the development of hamartomatous lesions in multiple organs, including the brain, kidneys, skin, heart, and lungs [1].

The clinical presentation is heterogeneous with neurological, dermatological, renal, cardiac, and pulmonary manifestations. Renal involvement is a major cause of morbidity and mortality, with angiomyolipomas being the most common renal manifestation. Renal cysts are less frequent but may be associated with more severe disease and progressive renal dysfunction [1, 2].

Diagnosis is based primarily on established clinical criteria, while molecular genetic testing supports diagnostic confirmation, genetic counseling, and characterization of phenotypic variability (2). Treatment is largely symptomatic. Epilepsy is commonly managed with vigabatrin, hormonal therapy, and, in selected cases surgery; however, drug-resistant epilepsy remains common and is associated with an increased risk of cognitive impairment [3].

The introduction of mTOR pathway inhibitors, particularly everolimus, has expanded therapeutic options for TSC. In addition to its established efficacy in subependymal giant cell astrocytoma and renal angiomyolipomas, everolimus may have a role in preserving renal function, particularly when initiated early [3, 4].

The LRP5 gene has also been proposed as a potential genetic modifier of cystic and liver disease, and may contribute to phenotypic variability in polycystic kidney disease [5].

Case presentation

At 7 months of age, the patient was hospitalized for episodes of staring, lethargy, and intermittent limb twitching. Brain magnetic resonance imaging showed findings consistent with TSC, without subependymal giant cell astrocytoma (SEGA). Renal ultrasonography demonstrated bilaterally enlarged kidneys with multiple cysts, without angiomyolipomas. Three hypopigmented skin lesions were also observed, and the diagnosis of TSC was established based on two major and one minor diagnostic criteria.

Genetic analysis showed no abnormalities in TSC1 and TSC2 exon copy number. Subsequent next-generation sequencing (NGS) identified a heterozygous missense variant in the LRP5 gene, NM_002335.4.3279C > G, p.(Ile1093Met), resulting in the substitution of isoleucine with methionine at position 1093. Variants in LRP5 have been associated with polycystic liver disease and may also be associated with renal cystic involvement.

During follow-up, the patient was monitored by a multidisciplinary team. Echocardiographic and ophthalmological examinations were unremarkable. Due to epileptic seizures, multiple antiseizure medications. Serial renal imaging demonstrated progressive enlargement of both kidneys and increasing cystic changes. Abdominal MRI additionally revealed a small hepatic cystic lesion in segment III of the left hepatic lobe.

At 4 years of age, treatment with everolimus (5 mg/day) was initiated despite the absence of SEGA or renal angiomyolipomas, based on available literature at that time suggesting a potential beneficial effect of mTOR inhibitors on the development and progression of renal manifestations in tuberous sclerosis complex. Everolimus therapy was continued for three years; however, no effect on the progression of the renal cystic changes was observed. During the follow-up period, a continuous increase in the size of both kidneys was documented. Renal function remained preserved throughout the observation period, with no evidence of proteinuria or microalbuminuria.

Kidney dimensions measured by abdominal MRI before and after initiation of everolimus therapy are presented in Table 1.

Table 1

Kidney dimensions, maximum cyst size, and hepatic cyst size on abdominal MRI[1]

Age	Kidney dimensions		Maximum cyst size		Hepatic cyst size
	Left	Right	Left	Right	
2 years	177x108x86mm	160x93x92mm	65mm	62mm	Cyst in the left hepatic lobe (S3) 16x7,6x11,5mm
3 years	183x112x88,8mm	163x107x95,6mm	77mm	51mm	Cyst in the left hepatic lobe (S3) 16x8,8x13,2mm
4,5 years	178x108x94mm	160x109x84mm	77mm	51mm	Cyst with no change in size
7 years	190mmx112x104mm	175x116x85mm	84mm	54mm	Cyst in the left hepatic lobe (S3) 14x11mm

Discussion

TSC is an autosomal dominant disorder characterized by the development of hamartomas in multiple organs. Renal involvement occurs in more than 80% patients, most commonly as angiomyolipomas and cystic kidney disease [1, 2].

In our patient, the diagnosis of TSC was established based on two major and one minor diagnostic criteria. Although molecular confirmation is not required, pathogenic variants in TSC1/TSC2 are not identified in all clinically diagnosed patients [6]. In our patient, NGS did not identify pathogenic variants in these genes but identified a heterozygous LRP5 variant. According to the Leiden Open Variation Database (LOVD), updated in January 2026, 494 individuals with LRP5 variants have been reported to date, with 644 unique DNA variants identified [7]. LRP5 variants are primarily associated with bone ocular disorders, while renal cysts involvement has been reported only sporadically and is not considered a characteristic manifestation of LRP5-associated disease [5].

Although cardiac and ophthalmological abnormalities are recognized manifestations of TSC [8, 9], both examinations were unremarkable in our patient.

mTOR inhibitors, particularly everolimus, have become an important therapeutic option in TSC and may have beneficial effects on several disease manifestations, including renal involvement [4, 10]. In our patient, everolimus was initiated at 4 years of age because of significant cystic renal involvement, despite the absence of SEGA or angiomyolipomas. However, during 3.5 years of treatment, progressive enlargement of both kidneys and progression of renal cystic changes were observed, while renal function remained preserved. However, during the subsequent 3.5 years of treatment, no slowing of kidney enlargement or reduction in the number of renal cysts was observed (Table 1).

Banerjee et al. described three patients with TSC and renal cystic disease treated with everolimus. Renal cystic changes were detected during infancy in all three patients, and everolimus was initiated between 2.5 and 3 years of age, primarily because of SEGA or progressive renal involvement. During treatment, a marked reduction or complete disappearance of renal cysts was observed in all cases. This was accompanied by improvement in renal function, with normalization of creatinine levels and increased estimated glomerular filtration rate (eGFR) [4].

In contrast, our patient demonstrated progression in both the number and size of renal cysts despite everolimus therapy, although renal function has remained preserved to date. These findings raise the possibility that the presence of the LRP5 variant may have contributed to the renal phenotype or that the initiation of everolimus at 4 years of age may have influenced the therapeutic response. However, these possibilities remain speculative.

To our knowledge, no previous cases of TSC associated with an LRP5 variant have been reported in the literature. Therefore, it is not possible to establish with certainty whether the identified LRP5 variant contributed to the pronounced renal phenotype observed in our patient or to the lack of an apparent response to everolimus therapy. The variant may represent an incidental finding or, alternatively, a potential genetic modifier of the phenotypic expression of TSC. Further functional and clinical studies are required to clarify its potential role.

Further research is warranted to elucidate the contribution of additional genetic factors and to determine the long-term effects of mTOR inhibition on renal function and the progression of cystic kidney disease in patients with TSC.

Declarations

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Vesna Stojanović, Milica Kovačević, Nina Brkić, Dragana Simić, Maja Samardžić Lukić, Nataša Kovač, Marijana Savin and Aleksandra Milutinović. The first draft of the manuscript was written by Vesna Srojanović, Milica Kovačević and Nina Brkić, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Approval was obtained from the ethics committee of University of Novi Sad and Institute for Child and Youth Healthcare of Vojvodina. The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

Written informed consent was obtained from the parents.

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Footnotes

1. The darker-shaded area of the table represents kidney and hepatic cyst dimensions measured after initiation of everolimus therapy.