Koç *et al.*
Egyptian Pediatric Association Gazette (2024) 72:70
https://doi.org/10.1186/s43054-024-00310-1

Egyptian Pediatric Association Gazette

CASE REPORT Open Access

Mechanism of renal cyst formation in a child with tuberous sclerosis complex: a case report

Ece Koç[1], Emre Leventoğlu[2*], Akif Kavgacı[3], Alev Elçi Karaduman[3], Tuğba Hirfanoğlu[3] and Kibriya Fidan[2]

Abstract

Background Tuberous sclerosis complex (TSC) is a multisystem genetic disorder characterized by the development of benign tumors in various organs, including the brain, kidneys, heart, lungs, skin, and eyes. Herein, an infant who was followed up with a diagnosis of TSC and multiple cysts which were found in the kidneys was presented, and the mechanism of renal cyst formation in TSC was elucidated.

Case presentation An infant was referred to our hospital after delivery due to multiple cardiac homogeneous echogenicity in the antenatal period. Transthoracic echocardiography showed multiple rhabdomyomas in both ventricles. Three months later, she started to have seizures 1–3 times a day. Electroencephalography was compatible with active multifocal epileptic disorder and hypsarrhythmia. Brain magnetic resonance imaging revealed a thin corpus callosum, cortical and subcortical tubercles, and multiple subependymal nodules. Abdominal ultrasound revealed a multiloculated cyst reaching 1 cm in size in the liver, and multiple cortical cysts smaller than 6 mm were observed in both kidneys, in accordance with autosomal dominant polycystic kidney disease (ADPKD). Pathogenic deletions between 31–42 exons in *TSC2* gene and 28–46 exons in *PKD1* gene were detected, and the patient was diagnosed as PKD1/TSC2 contiguous gene deletion syndrome.

Conclusion The coexistence of TSC and ADPKD is a rare occurrence but has been documented. Regular follow-up visits with healthcare providers, including nephrologists, cardiologist, neurologists, dermatologists, and other specialists as needed, are essential for the comprehensive management of coexistence of TSC and ADPKD. Individualized treatment plans should be developed based on the specific needs and manifestations of each patient, with a focus on optimizing outcomes and improving quality of life.

Keywords Tuberous sclerosis complex, Autosomal dominant polycystic kidney disease, Contiguous gene syndrome

Background

Tuberous sclerosis complex (TSC) is a multisystem genetic disorder characterized by the development of benign tumors in various organs, including the brain, kidneys, heart, lungs, skin, and eyes. It is caused by mutations in either the *TSC1* gene (encoding hamartin) or the *TSC2* gene (encoding tuberin), leading to dysregulation of the mammalian target of rapamycin (mTOR) signaling pathway. The resulting abnormal cell growth and proliferation underlie the diverse clinical manifestations of the disease [1, 2].

Herein, an infant who was followed up with a diagnosis of TSC and multiple cysts which were found in the kidneys was presented, and the mechanism of renal cyst formation in TSC was elucidated.

*Correspondence:
Emre Leventoğlu
dremrelevent@gmail.com
[1] Department of Pediatrics, Faculty of Medicine, Gazi University, Ankara, Turkey
[2] Department of Pediatric Nephrology, Faculty of Medicine, Gazi University, Ankara, Turkey
[3] Department of Pediatric Cardiology, Faculty of Medicine, Gazi University, Ankara, Turkey

Case presentation

A 3335-g female infant was born to an unrelated parent. She was referred to our hospital after delivery due to multiple cardiac homogeneous echogenicity in the antenatal period. Her Family history was unremarkable, and both parents and her older sister had no rhabdomyosarcoma or other abnormalities. At 3 months of age, his height was 63 cm (1.26 SDS), and his weight was 6.6 kg (1.08 SDS). Physical examination revealed hypopigmented macules on trunk. Transthoracic echocardiography showed a secundum defect in the interatrial septum and echogenic homogeneous structures as 9×4 mm in diameter in the interventricular septum, 3×6 mm in the right ventricle, 3×6 mm in the right ventricular outflow tract, and multiple rhabdomyomas towards the ventricular outflow tract in the left ventricle. Three months later, she started to have seizures 1–3 times a day, lasting several seconds, with tonic contractions of the extremities. Electroencephalography was compatible with active multifocal epileptic disorder and hypsarrhythmia. Extensor spasm was observed during the seizure. The patient was started on vigabatrin treatment, and brain magnetic resonance imaging revealed a thin corpus callosum, cortical and subcortical tubercles, and multiple subependymal nodules (Fig. 1). The patient was evaluated by pediatric cardiology and neurology departments, and genetic analysis was studied with a preliminary diagnosis of TSC. A pathogenic heterozygous deletion between 31 and 42 exons in *TSC2* gene was detected in targeted next-generation sequencing for *TSC1* and *TSC2* genes. The patient was diagnosed as TSC type 2.

Abdominal ultrasound performed for additional anomalies revealed a multiloculated cyst reaching 1 cm in size in the liver. The right kidney was 58×23 mm, and the left kidney was 53×23 mm in size. Bilateral renal parenchymal echogenicity increased, and corticomedullary differentiation disappeared. Multiple cortical cysts smaller than 6 mm were observed in both kidneys, in accordance with autosomal dominant polycystic kidney disease (ADPKD) (Fig. 2). The patient was referred to the Department of Pediatric Nephrology. Targeted next-generation sequencing analysis for cystic kidney diseases revealed a heterozygous deletion in exons 28–46 of the *PKD1* gene. Therefore, the patient was diagnosed as PKD1/TSC2 contiguous gene deletion syndrome.

During follow-up, clinical seizure did not recur under vigabatrin, and she was compatible with her age neurodevelopmentally. At 14 months of age, she was found

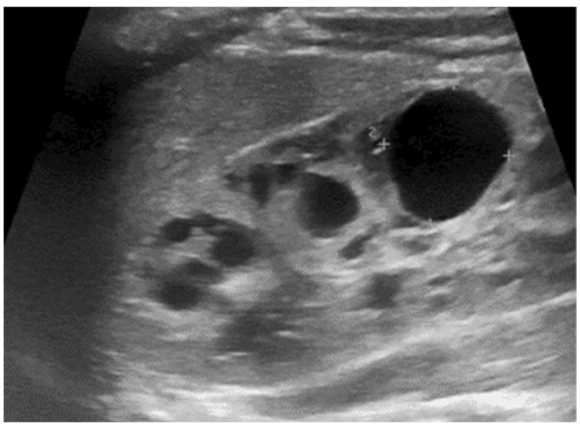

Fig. 2 Image of urinary ultrasound of the patient. Increased parenchymal echogenicity and multiple parenchymal cystic lesions in the right kidney

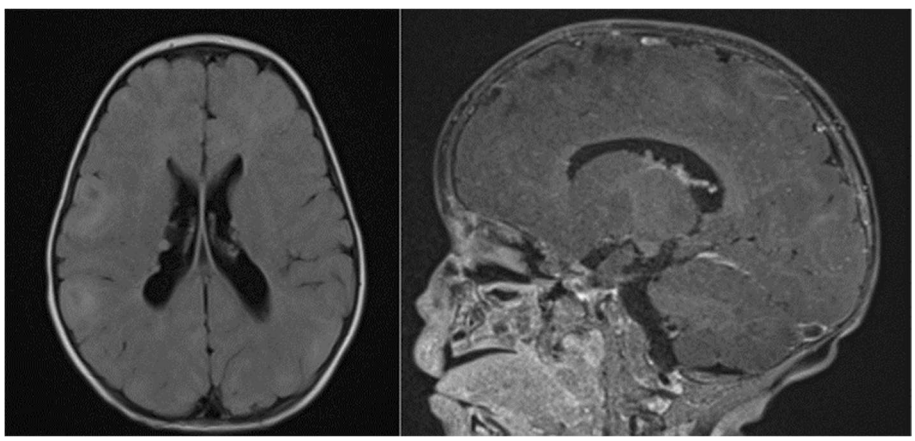

Fig. 1 Images of cranial MRI of the patient. The corpus collosum is thin. The lateral ventricles are wide, especially in their posterior part. Contour lobulation is observed in the superior wall of the right lateral ventricle. Numerous subependymal millimeter-sized nodular lesions were noted on the lateral ventricular walls. There is an appearance of tubercles affecting the cortex-subcortical areas, which are widespread in both cerebral hemispheres, especially in the frontal and parietal lobes

to be hypertensive (114/68 mmHg, > 99th) during routine outpatient clinic examination. Her height was 76 cm (−0.82 SDS) and weighed 10 kg (−0.08 SDS). Kidney function tests were normal, and there was no hematuria or proteinuria. On ultrasound, both were larger than normal in size (right kidney 125×63 mm, left 131×70 mm). There were multiple parenchymal cystic lesions in both kidneys, the largest on the left (approximately 45×40 mm in size). In addition, a hyperechoic nodular lesion 10×7 mm in size, angiomyolipoma, was observed in the lower pole of the right kidney. Since angiotensin-converting enzyme inhibitors are used as the drug of choice to control blood pressure in cystic kidney disease [3], the patient was planned to start enalapril; however, normotension was maintained with amlodipine and propranolol until bilateral renal artery stenosis was excluded. Subsequent renal Doppler imaging did not reveal any appearance compatible with stenosis, and therefore, a gradual replace of the current medications to enalapril was planned with close follow-up.

Discussion

The coexistence of TSC and ADPKD is a rare occurrence but has been documented. This association is defined as contiguous gene syndrome [4]. TSC is caused by mutations in either the *TSC1* or *TSC2* gene, leading to dysregulation of the mTOR signaling pathway. This dysregulation results in abnormal cell proliferation and differentiation, leading to the formation of benign tumors like hamartoma, angiomyolipoma, and cystadenoma in various organs. In addition, it may manifest as the development of cysts in the kidney [1].

ADPKD is caused by mutations in the *PKD1* or *PKD2* gene, which encode for proteins involved in the structure and function of primary cilia. Primary cilia are microtubule-based structures present on the surface of most cell types, including renal tubular epithelial cells. Dysfunction of primary cilia disrupts various signaling pathways, including the cyclic adenosine monophosphate pathway, leading to aberrant cell proliferation and fluid secretion. This results in the formation and progressive enlargement of multiple renal cysts, eventually leading to kidney enlargement and functional decline [3].

While TSC and ADPKD are caused by mutations in different genes (*TSC1/TSC2* and *PKD1/PKD2*), there may be genetic interactions or common pathways that predispose individuals to the development of both conditions. The dysregulation of common signaling pathways, such as the mTOR pathway, could contribute to the development and progression of renal cysts [5]. Therefore, kidney cysts are seen in 30–50% of TSC patients [4].

Conclusion

As seen in adjacent gene syndrome, such as TSC and ADPKD, a pathology in one gene can affect the function of a neighboring gene and lead to the addition of new clinical features to the existing phenotype. In such diseases affecting different subspecialties, regular follow-up visits with healthcare providers, including nephrologists, cardiologist, neurologists, dermatologists, and other specialists as needed, are essential for the comprehensive management of coexistence of TSC and ADPKD. Individualized treatment plans should be developed based on the specific needs and manifestations of each patient, with a focus on optimizing outcomes and improving quality of life. We would also like to emphasize that family screening should not be forgotten in order to diagnose such diseases, which have a genetic basis, in the asymptomatic period.

Acknowledgements
We thank the parents who gave permission for their child's medical information to be used for this manuscript.

Authors' contributions
EK analyzed and interpreted patient data on TSC and ADPKD. AK performed the cardiac evaluation of the patient. AEK and TH managed the neurologic follow-up and treatment of the patient. EL and KF performed the evaluation of the patient's renal involvement and contributed significantly to the writing of the manuscript. All authors read and approved the final manuscript.

Funding
The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This article presents a case report involving a pediatric patient with a tuberous sclerosis complex and autosomal dominant polycystic kidney disease. The study complied with the ethical principles outlined in the Declaration of Helsinki. Written informed consent was obtained from the patient's parents to publish their cases and accompanying images. The need for ethics approval was waived by the Hospital Inner Committee, as per their guidelines. The confidentiality of patient information was strictly maintained, and all data were de-identified. This study adheres to the ethical standards of our institution and ensures the privacy and rights of the patients involved.

Consent for publication
Written consent to publish had been obtained from the parents.

Competing interests
The authors declare that they have no competing interests.

Received: 24 May 2024 Accepted: 27 June 2024
Published online: 20 September 2024

References

1. Islam MP (2021) Tuberous sclerosis complex. Semin Pediatr Neurol 37:100875

2. Henske EP (2005) Tuberous sclerosis and the kidney: from mesenchyme to epithelium, and beyond. Pediatr Nephrol 20:854–857
3. Martínez V, Furlano M, Sans L et al (2022) Autosomal dominant polycystic kidney disease in young adults. Clin Kidney J 16:985–995
4. Gallo-Bernal S, Kilcoyne A, Gee MS, Paul E (2023) Cystic kidney disease in tuberous sclerosis complex: current knowledge and unresolved questions. Pediatr Nephrol 38:3253–3264
5. Soleimani M (2023) Not all kidney cysts are created equal: a distinct renal cystogenic mechanism in tuberous sclerosis complex (TSC). Front Physiol 14:1289388

Publisher's Note