ISSN: 2757-6817

Unika Sağlık Bilimleri Dergisi
Unika Journal of Health Sciences

Derleme/Review Article

Developmental and Genetic Foundations of Kidney and Urinary Tract Anomalies: An Anatomical and Clinical Exploration of CAKUT

Böbrek ve İdrar Yolu Anomalilerinin Gelişimsel ve Genetik Temelleri: CAKUT'un Anatomik ve Klinik İncelemesi

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Abstract: Congenital anomalies of the kidney and urinary tract (CAKUT) describe a broad spectrum of diseases resulting from aberrant development of the renal parenchyma, urinary collecting system, lower urinary tract, or kidneys during embryonic stages. Higher percentages of patients with CAKUT have lower urinary abnormalities, such as vesicoureteral reflux (25%), ureterovesical junction obstruction (11%), and ureteropelvic junction obstruction (25%). Kidney abnormalities are known to be prevalent throughout the prenatal period, making up roughly 20–30% of all detected anomalies. The term "CAKUT" refers to a group of diseases that include multiple cystic dysplastic kidneys and mild unilateral hydronephrosis. The prognosis of those with CAKUT can differ significantly; while some individuals may have ideal kidney function, others may experience chronic kidney disease requiring dialysis and kidney transplantation. There are still negative opinions about the etiology of CAKUT. Although familial clustering is common, many CAKUT instances are sporadic, indicating that genetic variables may influence CAKUT characteristics. Numerous studies focusing on embryology have shed light on the genetic components of CAKUT, but research in this area is ongoing. This study comprehensively explores the critical stages of embryonic kidney development and different types of CAKUT. Additionally, it examines long-term monitoring and treatment modalities for CAKUT patients It also examines the long-term monitoring and treatment methods of CAKUT patients in the literature.
Keywords: Congenital kidney anomalies, Urinary tract developmental disorders, CAKUT, Kidney development.

Öz: Konjenital böbrek ve idrar yolu anomalileri (CAKUT), embriyonik dönemlerde böbrek parankiminin, idrar toplama sisteminin, alt idrar yollarının veya böbreklerin anormal gelişiminden kaynaklanan geniş bir hastalık yelpazesini tanımlar. CAKUT hastalarının yüksek yüzdeleri, vesikoureteral reflü (%25), üreterovesikal bileşke tıkanıklığı (%11) ve üreteropelvik bileşke tıkanıklığı (%25) gibi alt idrar yolu anomalilerine sahiptir. Böbrek anomalileri, prenatal dönem boyunca yaygın olarak görülmekte olup, tüm tespit edilen anomalilerin yaklaşık %20-30'unu oluşturur. CAKUT terimi, birden fazla kistik displastik böbrek ve hafif unilateral hidronefroz gibi hastalıkları içeren bir grup hastalığı tanımlar. CAKUT olanların prognozu önemli ölçüde farklılık gösterebilir; bazı kişiler ideal böbrek fonksiyonuna sahip olabilirken, diğerleri kronik böbrek hastalığı yaşayabilir ve sonunda diyaliz ve böbrek nakli gerekebilir. CAKUT etiyolojisi hakkında hala olumsuz görüşler mevcuttur. Ailevi kümelenme yaygın olsa da birçok CAKUT örneği sporadik olduğundan, genetik değişkenlerin CAKUT özelliklerini etkileyebileceği düşünülmektedir. Embriyolojiyi içeren birçok çalışma CAKUT'un genetik bileşenleri üzerine ışık tutmuş, ancak bu alandaki araştırmalar devam etmektedir. Bu çalışma, CAKUT'un embriyonik böbrek gelişimindeki kritik aşamaları ve farklı CAKUT tiplerini detaylı bir şekilde ele almaktadır. Ayrıca, literatürdeki CAKUT hastalarının uzun vadeli izleme ve tedavi yöntemlerini de incelemektedir.
Anahtar kelimeler: Konjenital böbrek anomalileri, İdrar yolu gelişim bozuklukları, CAKUT, Böbrek gelişimi.

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Makale Gönderim:09.05.2024 Makale Kabul:02.07.2024 Makale Yayın:30.04.2025

Introduction

Congenital anomalies of the kidney and urinary tract (CAKUT) describe a broad spectrum of diseases resulting from aberrant development of the renal parenchyma, urinary collecting system, lower urinary tract, or kidneys during embryonic stages. Higher percentages of patients with CAKUT have lower urinary abnormalities, such as vesicoureteral reflux (25%), ureterovesical junction obstruction (11%), and ureteropelvic junction obstruction (25%) (Stonebrook et al., 2019).

Kidney abnormalities are known to be prevalent throughout the prenatal period, making up roughly 20–30% of all detected defects (Stonebrook et al., 2019). The term "CAKUT" refers to a group of diseases that include multiple cystic dysplastic kidneys and mild unilateral hydronephrosis. For those who have CAKUT, the prognosis can differ significantly. While some people may have ideal kidney function and their daily activities are unaffected, others may experience chronic renal disease and eventually kidney failure that requires dialysis and kidney transplantation (Walker et al., 2023).

The etiology of CAKUT remains poorly understood. Although familial clustering is common, many CAKUT instances are sporadic, indicating that genetic variables may influence CAKUT characteristics (Fletcher et al., 2013; Stonebrook et al., 2019).

Embryology of the Kidney

In humans and other mammals, the development of the kidneys is a multistage, intricate process that moves from the anterior to the posterior. In humans, this process begins at approximately embryonic day 22, when the nephric duct develops in the intermediate mesoderm. The kidneys subsequently start developing in the nearby mesoderm as a result of the nephric duct's caudal extension. The pronephros, mesonephros, and metanephros are the three separate phases or segments from which the embryonic kidneys emerge from the intermediate mesoderm (Dos Santos Junior et al., 2014; Stonebrook et al., 2019). All parts of the nephron derive from the metanephric mesoderm. Initially, this tissue forms primitive renal tubules, which undergo maturation over time (Seely, 2017; Stonebrook et al., 2019). The fetal kidney begins its development in the pelvis or sacral region and later moves upwards to its adult position in the thoracolumbar region (between the T12 and L3 vertebrae) within the retroperitoneal fossa. When the kidney reaches the retroperitoneal fossa, it rotates 90 degrees to the medial side, ultimately reach its final position by the eighth week of pregnancy (Dos Santos Junior et al., 2014; Stonebrook et al., 2019).

During the prenatal stage, the role of the kidney is to maintain the amniotic fluid. Once the gestation reaches 16 weeks, the primary source of amniotic fluid shifts to fetal urine. Consequently, the volume of amniotic fluid can serve as a potential indicator for irregular renal development. However, it is only after birth that the kidney commences its regulation of fluid, electrolyte, and acid-base balance, and waste excretion (Stonebrook et al., 2019; Takeuchi et al., 1994).

Types of Congenital Anomalies of the Kidney and Urinary Tract

Renal Hypoplasia

Renal hypoplasia occurs when one or both kidneys are entirely absent, with no identifiable rudimentary tissue present. This condition arises from the failure of metanephros formation and is frequently accompanied by the absence of the ureter on the same side (Dos Santos Junior et al., 2014; Seely, 2017).

Both research in animals and observations in clinical settings have revealed a range of factors contributing to this condition. Renal agenesis, along with several other developmental kidney abnormalities, tends to be more prevalent in males compared to females (Westland & Schreuder, 2014). Unilateral renal agenesis is often without symptoms and is commonly detected incidentally. In contrast, bilateral renal agenesis causes significant oligohydramnios and can lead to fetal or perinatal loss. Furthermore, renal agenesis may coincide with abnormalities in other organ systems, affecting both neighboring structures , as well as distant structures like central nervous system (Dos Santos Junior et al., 2014; Toka et al., 2010).

Ultrasound scans can identify fetal kidneys in the early stages of pregnancy (10 and 12 weeks), enabling the prenatal detection of renal agenesis. When diagnosis is uncertain, computed tomography and radionuclide studies offer useful support. A compensatory hypertrophy may occur in cases of unilateral renal agenesis, resulting in the remaining kidney growing to the 95th percentile of gestational age (Chow et al., 2005; Urisarri et al., 2018).

It is crucial to confirm that the kidney that is not visible is not positioned abnormally or exhibiting dysplasia symptoms. Therefore, pelvic ultrasound is frequently advised. Magnetic resonance imaging is also employed as a confirmatory diagnostic tool (Stonebrook et al., 2019).

During the first assessment of a patient with a single kidney, it is crucial to gather a comprehensive medical history and conduct a thorough physical examination. This is conducted to evaluate the potential presence of extrarenal congenital anomalies (Toka et al., 2010). Prenatal chromosomal microarray analysis has not demonstrated any additional benefits

compared to the general population (Sagi-Dain et al., 2018). From birth onwards, it is important to closely monitor the growth charts of these patients for any signs of abnormal or poor growth, as this can indicate renal insufficiency. Long-term complications may include the development of chronic kidney disease due to prolonged compensatory glomerular hyperfiltration. Hence, it's essential to routinely check blood pressure and conduct urinalysis to detect high blood pressure and proteinuria. The presence of either of these symptoms may suggest damage to the single kidney, necessitating a serum creatinine test to determine the glomerular filtration rate (GFR) (Westland & Schreuder, 2014). It has been noted that individuals who are overweight or obese face an increased risk of developing kidney diseases (Gonzalez et al., 2005; Kovesdy et al., 2017). As per the 2012 guidelines issued by the American Academy of Pediatrics, having a single kidney does not necessarily mean one should avoid participating in contact sports (Grinsell et al., 2012).

Ectopic Kidney

Ectopic kidneys, often located in the pelvic region, occur due to errors in the process of ascent. There have been rare cases reported of thoracic kidneys (N'Guessen et al., 1984). Ectopic kidneys may occur unilaterally or bilaterally. A "pancake kidney" is a mass of kidney tissue with two distinct renal pelvises and a different number of ureters when both kidneys are located in the pelvic region and are connected to each other. An ectopic kidney characterised by a ureter that crosses the midline is called a crossed fused ectopia. Typically, these kidneys are smaller and underdeveloped. As a result, compensatory hyperfiltration and hypertrophy may occur in the remaining kidney (Dos Santos Junior et al., 2014; Guarino et al., 2004).

Ectopic and pelvic kidneys typically remain asymptomatic. In the past, autopsies have revealed a higher prevalence of these conditions compared to clinical diagnoses. However, advancements in ultrasound technology have altered this trend, and its current impact remains uncertain. If an ectopic kidney is identified during prenatal ultrasound, a postnatal renal ultrasound is suggested to verify its pelvic location. Although certain studies indicate no effect on blood pressure and kidney function, it's recommended to conduct regular monitoring with annual serum creatinine tests, urinalysis, and blood pressure assessments for surveillance and preventive measures (Van Den Bosch et al., 2010).

Like renal hypoplasia, long-term complications might involve chronic kidney disease stemming from prolonged compensatory glomerular hyperfiltration. Alterations in blood pressure and/or renal function could signal renal insufficiency. (Westland & Schreuder, 2014).

Renal Fusion (Horseshoe Kidney)

A renal parenchymal or fibrous isthmus is formed when kidneys fuse at their lower poles, a condition known as horseshoe kidney. Abnormal migration of nephrogenic cells during embryonic development is believed to cause horseshoe kidney with a parenchymal isthmus. The majority of horseshoe kidneys are located at lower vertebral levels in the pelvis. As the kidneys ascend, the connecting isthmus gets lodged behind the inferior mesenteric artery. Early fusion may result in higher ureter insertion sites and malrotation, which may impede the ureteropelvic junction and cause obstructive uropathy (Dos Santos Junior et al., 2014; Seely, 2017).

Horseshoe kidneys are found in around 1 in 500 live births, with a higher occurrence in males. They usually do not cause symptoms and are frequently detected incidentally during prenatal ultrasound scans. However, individuals with horseshoe kidneys may encounter complications such as ureteropelvic junction obstruction, which can result in conditions like hydronephrosis, urinary tract infections (UTIs), and nephrolithiasis. Horseshoe kidneys are also frequently associated with renal tumors, especially Wilms tumor, and may be linked to other genitourinary anomalies (Petrović et al., 2012; Tkocz & Kupajski, 2012). There is insufficient evidence supporting the efficacy of proactive sonographic screening. Surgical removal of horseshoe kidneys can pose challenges due to abnormal blood vessel configuration and the kidney's position (Yecies et al., 2016).

Polycystic Kidney Disease

Polycystic kidney diseases encompass a diverse range of conditions that can manifest either during fetal development or remain asymptomatic until adulthood. The identification of genes associated with cystic kidney diseases and their corresponding proteins has provided researchers with crucial targets for investigating the underlying mechanisms and consequences of these conditions (Malekshahabi et al., 2019; Shin & Park, 2016). Among these conditions, autosomal dominant polycystic kidney disease (ADPKD) stands out as the most prevalent inherited renal disorder, caused by mutations in either the PKD1 (primary) or PKD2 (secondary) genes. ADPKD is the third leading cause of end-stage kidney disease, trailing only diabetes mellitus and hypertension in prevalence (Seikaly et al., 2003). By age 70, about half of patients with ADPKD require either dialysis or a kidney transplant (Churchill et al., 1984).

The identification of ADPKD primarily depends on kidney imaging. Common observations include enlarged kidneys with multiple cysts distributed on both sides. In children

aged 0 to 5 years, who have a familial history of ADPKD, the presence of a single cyst is sufficient for the diagnosis (Chapman, 2007). Ultrasonography is the imaging technique most frequently used due to its cost-effectiveness and safety. However, in certain cases, genetic testing may be necessary for a definitive diagnosis. As the condition advances, the kidneys usually enlarge, often reaching more than five times their normal size in the period leading up to kidney function decline. Assessing kidney volume is the most dependable indicator for predicting the onset of renal insufficiency (Tangri et al., 2017). Additional renal symptoms may include high blood pressure, UTIs, difficulties in concentrating urine, kidney stones, blood in urine, protein in urine, as well as abdominal or flank discomfort. The seriousness of these issues correlates with the degree of cysts affecting the kidneys (Subramanian & Ahmad, 2019).

Histologically, cysts in the kidneys begin in the tubular segments and gradually grow along the nephron, ultimately resulting in kidney dysfunction (Halvorson et al., 2010). ADPKD affects the entire body, and patients may encounter additional complications beyond the kidneys, such as cysts in other organs like the liver and pancreas, as well as cardiovascular issues like mitral valve prolapse and cerebral berry aneurysms. However, these extra renal effects are seldom seen in children.

Treatment for ADPKD, usually carried out by a nephrologist, focuses on addressing chronic kidney insufficiency, high blood pressure, urinary tract infections, and pain. In some instances, dialysis and kidney transplant may also be required in adolescent patients. Invasive procedures like percutaneous cyst aspiration and sclerosis, open or laparoscopic cyst decompression, and laparoscopic denervation may be utilized to manage pain. Nephrectomy might be warranted for patients with end-stage kidney disease and uncontrollable pain, recurrent urinary tract infections, or extremely enlarged kidneys that could hinder future transplantation (Stonebrook et al., 2019; Subramanian & Ahmad, 2019; Torra, 2019).

Multicystic Dysplastic Kidney

A type of renal dysplasia known as multicystic dysplastic kidney (MCDK) is typified by a disordered renal parenchyma and a large number of non-communicating cysts within the dysplastic kidney tissue. It is a commonly observed congenital urinary tract abnormality, occurring in approximately 1 in 3640 births (Feldenberg & Siegel, 2000).

Although MCDK usually occurs randomly, there have been reported cases of familial occurrences. It does not show a preference for one side of the body and is slightly more common in males. MCDK can manifest independently, co-occur with other abnormalities in the genitourinary system, or be linked to a genetic syndrome (Rudnik-Schöneborn et al., 1998).

Ultrasonography is a prevalent method for identifying MCDK, with approximately two-thirds of cases being suspected before birth. While children and adolescents with unilateral MCDK typically have favorable outcomes, those with bilateral MCDK often face oligohydramnios, which can result in fetal loss, or progress to end-stage renal disease during childhood. If MCDK is suspected during prenatal ultrasound, it's crucial to verify the diagnosis with a postnatal ultrasound. This initial postnatal ultrasound not only confirms the diagnosis but also enables screening for vesicoureteral reflux (VUR), abnormalities in the contralateral kidney, and genital abnormalities (Stonebrook et al., 2019).

Vesicoureteral Reflux

Vesicoureteral reflux is the term used to describe the backward flow of urine from the bladder back into the kidneys. It has been linked to renal injury occurring before birth and the development of UTIs, pyelonephritis, and additional kidney damage after birth. The exact prevalence of VUR remains uncertain as voiding cystourethrogram (VCUG) is not routinely conducted in healthy children. However, VUR has been identified in 8-50% of children and 36-49% of infants and newborns who underwent a VCUG after experiencing a UTI (Bates et al., 2016).

The majority of individuals diagnosed with VUR have encountered a UTI accompanied by fever. Moreover, VUR is frequently identified through prenatal ultrasound findings of hydronephrosis or hydroureter, in children with unilateral MCDK, or in those exhibiting notable bladder dysfunction (Stonebrook et al., 2019).

The voiding cystourethrogram is the most reliable method for diagnosing VUR. Because this procedure involves urethral catheterization and either radionuclide administration or fluoroscopy, it is considered invasive (Stonebrook et al., 2019).

The management of VUR encompasses both medical and surgical approaches. Medical intervention is predicated on the finding that low-grade VUR frequently goes away on its own. As part of this strategy, problems with the function of the bowel and bladder, metabolic disorders resulting from renal insufficiency, blood pressure control, proteinuria reduction, and routine radiological evaluations to track the condition may all be addressed. In certain patient populations, daily antibiotic prophylaxis for UTIs may be beneficial. Surgical intervention may be warranted if there are additional abnormalities in the upper or lower urinary tract or if recurrent UTIs occur (Stonebrook et al., 2019).

Ureterovesical Junction Obstruction

Ureterovesical junction obstruction (UVJO) is a condition characterized by an anatomical or functional abnormality in the distal segment of the ureter(Rabani & Mousavizadeh, 2017).

In children, UVJO is one of the common causes of obstructive uropathy, along with ureteropelvic junction obstruction (UPJO) (Chevalier, 2004). UVJO can lead to hydronephrosis and hydroureteronephrosis, affecting both children and adults (Di Fabrizio et al., 2024).

The etiology of the UVJO can be due to of various factors, including congenital abnormalities, acquired illnesses, and genetic factors (Ahram et al., 2023). UVJO can have diverse origins, including genetic factors that disrupt the morphogenesis of the urinary t or the functional aspects of the pyeloureteral peristaltic machinery (Ahram et al., 2023; Chen, 2009).

Studies have shown that UVJO can be associated with conditions like lupus cystitis, leading to distal ureteral obstruction at the ureterovesical junction (Liu & Fu, 2014). Furthermore, UVJO can lead to complications such as bilateral hydronephrosis, VUR, and even renal failure. The obstruction at the ureterovesical junction can cause reflux due to increased bladder internal pressure overcoming the junction (Enrique & Raquel, 2021).

UVJO can also be associated with lower urinary tract development abnormalities, such as defects in the antireflux mechanism and abnormal structure of the UVJ (Rasouly & Lu, 2013).

Ureteropelvic Junction Obstruction

Ureteropelvic junction obstruction is a condition characterized by a significant impairment of urinary transport at the ureteropelvic junction (UPJ) level, leading to functional or anatomical obstruction of urine flow from the renal pelvis to the ureter (Mehrazma et al., 2014). This obstruction can be caused by intrinsic factors such as congenital strictures, high ureteric insertion, irregular ureteral course, or extrinsic factors like aberrant vessels or fibrous bands compressing the ureter (Avanoglu & Tiryaki, 2020; Malhotra et al., 2022; Raviv et al., 1994).

UPJO is commonly considered a congenital anomaly, although it can also manifest as an acquired condition, especially in childhood (Cleveland et al., 1986; Uberoi et al., 2009).

The prevalence of UPJO is estimated to be around 1 in 1000 to 2000 neonates (Mehrazma et al., 2014). Embryologically, UPJO is closely related to CAKUT and is considered the most common and most investigated form of CAKUT (Avanoglu & Tiryaki, 2020). Smooth muscle cell apoptosis and defective neural development have been implicated in the pathogenesis of

congenital UPJO, suggesting potential new therapeutic targets for this condition (Kajbafzadeh et al., 2006). Additionally, changes in the extracellular matrix proteins, apoptosis, and c-kit positive cells play a role in the pathogenesis of UPJO (Özel et al., 2010).

Genetically, UPJO has been associated with familial cases, indicating a genetic component in some instances (Dabra et al., 2003). Studies have highlighted the importance of myocyte apoptosis and neural development defects in the genetic underpinnings of congenital UPJO (Kajbafzadeh et al., 2006).

Furthermore, animal models have been utilized to study the genetic basis of UPJO, shedding light on the renin-angiotensin system and other genetic factors involved in the development of this condition (Klein et al., 2011).

Posterior Urethral Valve

Posterior urethral valves (PUV) are a frequent cause of urinary tract blockage in children. They consist of obstructive membranous folds located in the posterior urethra and occur exclusively in male patients (Bingham & Rentea, 2021). Posterior urethral valves persist as a significant source of morbidity, mortality, and ongoing renal impairment in infants and children. Posterior urethral valves can cause a range of health issues affecting both the urinary system and the other systems. These complications include acute urinary retention, chronic kidney disease, and in severe instances, pulmonary hypoplasia due to reduced levels of amniotic fluid (Bingham & Rentea, 2021; Nasir et al., 2011). The precise cause of PUV is unclear, but it seems to be a complex genetic-mediated developmental disorder. While familial inheritance is rare, isolated cases have been documented (Nasir et al., 2011).

Conclusion

In summary, CAKUT comprises a range of conditions that affecting the kidney and/or urinary tract. Despite having different characteristics and clinical outcomes, they are related by a shared genetic foundation and molecular signaling pathways that affect kidney development. Due to the hereditary nature of many of these congenital abnormalities, progress in prenatal diagnostics, imaging, genetic testing, laboratory monitoring, and medical management has improved the prognosis and quality of life for impacted families.

Conflict of Interest: The authors declare no conflicts of interest.

Author Contributions: Idea: YZİY; Design: YZİY, NEŞ; Check: NEŞ, ŞT; Data collecting and/or Analysis: YZİY, NEŞ; Literature Review: YZİY, NEŞ; Critical Review: ŞT.

Peer Review: Internal/External independent.

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