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Congenital Anomalies of Kidney and the Urinary Tract. CAKUT Systemic Review

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Abstract:

The article describes Congenital Anomalies of Kidney and the Urinary Tract with emphasis on embryological basis, pediatric surgery and pediatric urology and covers a spectrum of lesions and their associations. The defects may be defects of kidney, ureter or both and associated with multiple Syndromic entities. The purpose of the article in addition is to find out latest mutations and genetic defects associated with this entity. Disruptions in signaling pathway are primarily responsible for CAKUT. Though there are varied and broad congenital anomalies which are seen, the article tries to put all the relevant information in a concise manner.CAKUT encompasses a very diverse and broad spectrum of malformations like renal agenesis, renal hypoplasia, Renal dysplasia,horse shoe kidneys, Ureteropelvic junction obstruction,Polycystic kidney syndromes, Mega ureters, Posterior urethral valves. It may present as an isolated entity or as a combination defect with malformations of other body systems

Aim: The aim of the article is to provide all updated and renewed information about CAKUT and the most possible associations it has been associated till date.
Method: Review of literature from all standard text, latest references from standard indexed journals taken to verify the associations.

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Result: Recent genetic and scientific advances suggest a significant number of new associations reported lately were noted in addition to revision of previous associations and their updates.

Conclusion: The CAKUT as a Syndromic entity is now recognized by Embryologists, Pediatricians, Neonatologists and Pediatric surgeons as a clinical entity of immense importance. Review of this Syndromic entity with most recent advances needs to be known by the most.New Mutations, newer genetic and defects in signaling pathway and migration defects along with multisystem associations not previously reported seem to be finding a ground in the pathogenesis of CAKUT.

Keywords: Metanephros, Bastema, Nephrogenic, mesoderm, ureteric, urethral, trisomies, cystic, Syndrome, dysplasia.

Introduction:

The development of the Urinary tract starts at fourth week with the formation of nephrogenic cord. Most parts of Urinary system are developed from Intermediate mesoderm[1]. Pronephros, Mesonephros and Metanephros are formed sequentially. Mesonephros has to regress and that is important for kidney development [2]. In humans kidney is predominantly Metanephric and Pronephros and Mesonephros don't play a dominant role in development. The excretory tubules are derived from the lowest part of nephrogenic cord. This part is the Metanephros. This part forms the nephrogenic blastema. The Ureteric Bud is responsible for formation of Collecting duct, Major/Minor Calyx,Metanephric Mesoderm forms the Renal Glomerulus**,**Bowman's capsule**,**PCT**,**DCTLoop Of Henle and the Collecting Tubule. The ureteric bud grows cranially towards the metanephric blastema. Once the cells of Metanephric blastema come in contact with ampulla derived from ureteric bud, nephronic differentiation is started. This is followed by ascent of the kidneys and medial rotation.At beginning of fifth week, metapephric blastema secretes a protein Glial cell derived neurotropic factor (Gdnf) inducing growth in Mesonephros known as Ureteric bud. Specifically Gdnf family receptor alpha 1 is strongly expressed in mesonephric duct. Eya1 acts as a critical regulator for metanephric mesenchyme[3]. Development of glomerulus begins by podocytes secreting VEGF2. Development of bladder and ureter begins simultaneously when the urogenital sinus divides the cloaca into to parts. The urogenital sinus forms the bladder and its inferior part forms the urethra. Mesoderm leads to development

Discussion:

It can be summarized that the kidneys, ureter and its vasculature are derived from the intermediate mesoderm. Mesoderm does not lead to development of parts of Urinary tract only. Other structures developed from mesoderm can also be affected in case of mesodermal defects at an early stage of fetal development. The smooth muscle of urinary bladder and its connective tissue are derived from Splanchopleuric mesoderm. The urethra and bladder are derived from endoderm and the neural crest forms the autonomic nervous system of urinary tract.

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It has been seen that signaling molecules and correct signaling is responsible for normal embryogenesis. The correct development of Pronephros, Mesonephros and Metanephros is mainly due to Lim1, Add1 and Pax 2/8. The initiation of Nephron development is mainly due to Pax 2.Some of the Pax 2/8 mutations can cause absence of kidney development due to failure of LIM 1 Expression. Humans carrying single Pax 2 mutant allele exhibit renal hypoplasia, vesicoureteric reflux and optic nerve colobomas [4].

Bone morphogenic protein (Bmp 4) and Gremlin in addition to Ddnf-RET Pathway regulate development of ureteric bud. Ureteric bud secretes Gremlin which inhibits Bmp 4 ensuring normal development[5]. Environmental factors associated with CAKUT are Folic acid use, Vitamin A deficiency, Maternal obesity, maternal diabetes, Maternal malnutrition in addition to the Syndromes mentioned.

Renal agenesis may be a manifestation of CAKUT. Agenesis may be unilateral or bilateral. Bilateral is incompatible with life. Renal agenesis is usually associated with oligohydraminos and Potters Syndrome. Unilateral agenesis causes Compensatory hypertrophy of the solekidney. Bilateral renal agenesis is found to be associated with mutations of RET, EYA1 and ANOS1 genes. This is in addition to deletion of chromosome 10q26 which is implicated in urogenital development [6].

Horse shoe kidneys may be a manifestation of CAKUT. They are commonly a result of Fusion anomaly. In most of the cases the upper poles are not fused but the lower poles. In most cases more than 90 percent fusion occurs at lower poles .Abnormalitiesin rotation ofembryoat the caudal end is also believed to play a part. This is supported by the fact that Lower vertebral defects are associated with Horse shoe kidney. Usually patients with Turners Syndrome have horse shoe kidney association along with other defects such asfemale phenotype, sexual infantilism, short stature,low set ears, multiple pigmented nevi, webbed neck, micrognathia, epicanthal folds, and shieldlike chest with microthelia, short fourth metacarpals, and cubitus valgus and cardiovascular defects such as Coarctation of Aorta.The Faulty ascent of the kidneys is thought to play a main role in development of horse shoe kidney. There is evidence of association of Horse shoe kidney with Edwards's syndrome and Downs's syndrome.Horse shoe kidneys may also be associated with Ureteropelvic junction obstructions, Vesicoureteral reflux, higher incidence of renal stones, malignancies like renal tumours, Wilms tumour in children and Transitional Cell cancers. Wilms tumour is more common including increase in rare tumours such as carcinoids[7].

CAKUT may present with Cystic in Kidneys. Polycystic kidneys can present as Autosomal Recessive Polycystic kidney or Adult Polycystic kidney disease. Autosomal Recessive Polycystic kidney Presents as multisystem Kidney which may cause Chronic flank pain or gross and microscopic hematuria.It is now considered as a Ciliopathy. The gene responsible has been located on chromosome 6.The disease may present with severe renal and

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Hepatobiliary disease.It occurs as a result of single gene named Polycystic kidney and hepatic disease (PKHD1) [8].

Adult Polycystic kidney disease is inherited as autosomal dominant in 90% cases. ADPKD commonly presents in 3rd – 4th decade of life. Clinical features are chronic flank pain,gross and microscopic hematuria, loss of Renal concentrating ability, Nephrolithiasis. Mutations in Short arm of chromosome 16 are responsible in many cases. There is an association with Intracranial Aneurysms, cysts in liver and pancreas as well as Mitral valve prolapse[9].

Posterior urethral valves: This is a very important cause of lower Urinary Tract Obstruction in case of male infants .They are mostly situated distal to verumontanum.They may be associated with distended urinary bladder, hydronephrosis and obstructive renal dysplasia.

CAKUT may present with Renal Hepatic Pancreatic dysplasia. There may be renal dysplasia along with cystic kidneys or cystic pancreas. NPNP3 gene and NEK8 gene mutations are responsible. Chromosomes 3 and 17 are primarily involved. It is associated with high mortality in early infancy and early childhood[10].

CAKUT may be associated with Meckel Gruber Syndrome. Patients may present with varied features such as multicystic dysplastic kidneys ,Renomegaly , encephaloceles and cleft palate. Gruber named this disease as Dysencephaliasplanchocysrica and mentioned that it was genetic [11] .

CAKUT may be associated with Jouberts Syndrome. Patients may present cystic dysplasia of kidneys, cerebellar hypoplasia, polydactyly and retinal dystrophy. Mutations in AH11, NPHP1, CEP 290, ARL13B, CC2D2A are primarily responsible[12].CAKUT may be associated with Caudal Dysplasia syndrome. This may be associated with renal agenesis, renal dysplasia and horse shoe kidneys, imperforate anus and hypoplasia of limbs . This condition is more common in case of diabetic mothers. CAKUT may be associated with BardetBiedl Syndrome[13]. Patients may present with cystic dysplasia of kidneys,Obesity, Retinitis pigmentosa and hypogenitalism. Mutations in BBS1 , BBS2, BBS4, CEP290, LTZFL1 are primarily responsible.CAKUT may be associated with VACTER –L Association[14]. Patients may present with dysplasia of kidneys in addition to vertebral defects, anal, cardiac malformations , trachea esophageal fistulae and limb anomalies are primarily responsible.

CAKUT may be associated with Zellweger Syndrome which is an uncommon autosomal recessive disorder characterized by features of abnormalities in brain gyri, horse shoe kidneys, urethral duplication, hypo plastic facial skeleton. It is a peroxiaomal disorder [15].

Cases of CAKUT have also been found in association with Renal Coloboma syndrome, Allagille syndrome, Towne Brokes syndrome , Otorenal Syndrome. In Otorenal syndrome there can be renal hypoplasia or bilateral renal agenesis [16].

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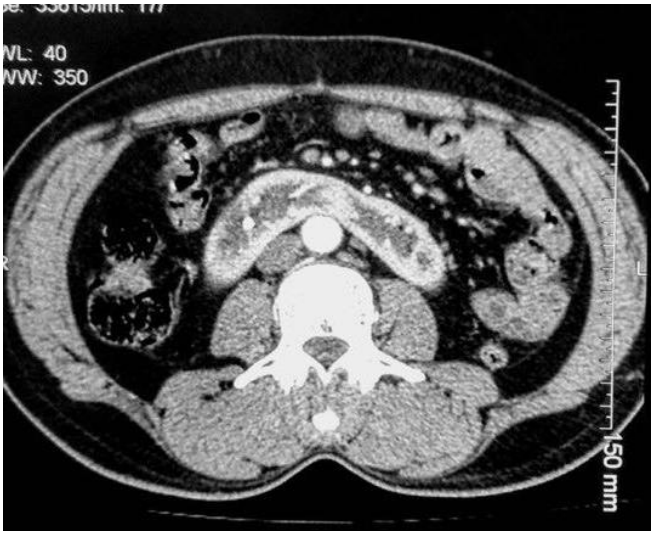
In the recent past CAKUT has been reported to have association with Ellis Van Creveld syndrome, Alstrom syndrome, Short rib Syndrome, Nephronopthisis and BardetCiedl syndrome [17, 18].

Result:

It is seen that Recent genetic and advances in embryology suggest a new associations reported lately were noted in addition to revision of previous associations and their updates.Mutations and Defects are associated with Lim1, Add1 and Pax 2/8, , HNF1B, SALL1, WT1, SIX1, EYA1 genes should be evaluated and Syndromic entities especially Renal Coloboma syndrome, Allagille syndrome, Towne Brokes syndrome , with Ellis Van Creveld syndrome, Alstrom syndrome, Short rib Syndrome, Otorenal Syndrome Turners Syndrome, Edwards syndrome and should be evaluated. Patients with defects of mesoderm and other syndromes may be associated with CAKUT.

Conclusion:

CAKUT imposes a great burden on affected children, their families and health care system. It may be complex and usually needs patient specific multidisciplinary approach. CAKUT is multifactorial and anEmbryologically significant entity relevant in Pediatric urology, Embryology, Neonatology and Genetics. Newer facts about CAKUT and associations and embryological and genetic basis of this entity are surfacing. New Mutations, newer genetic and defects in signaling pathway and migration defects along with multisystem associations not previously reported. As more and more cases are reported substantial statistical significance of such associations is noted. This increases the relevance of genetic basis and embryological basis of the disease and genetic testing can be a futuristic step and roper prenatal and postnatal management may prevent progression to End stage Kidney disease.



CT scan demonstrating Horse shoe kidney

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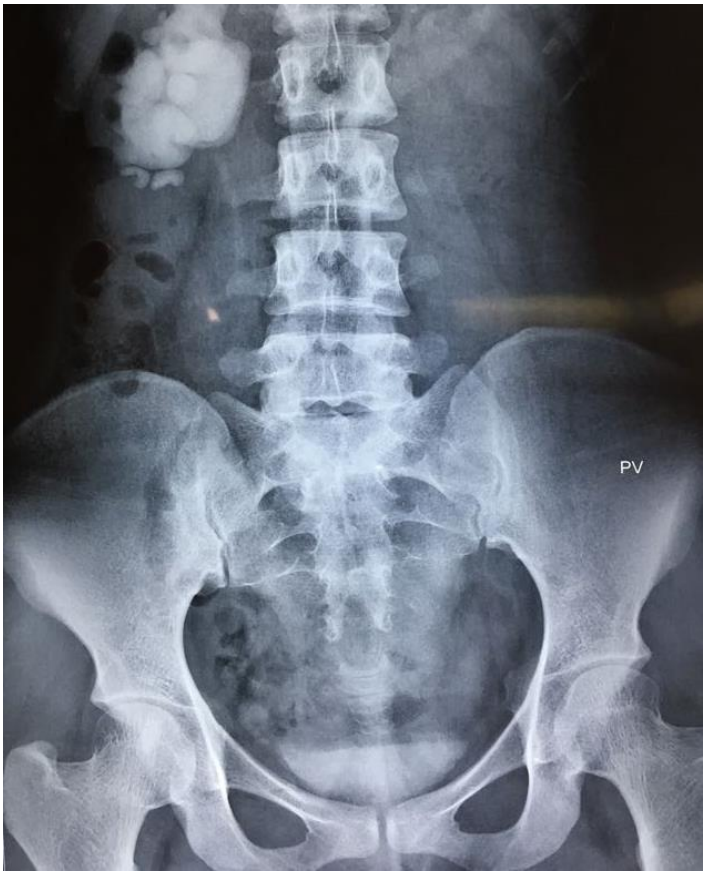

Radiograph demonstrating Pelviuretric junction obstruction.

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