Association Between Isolated External Ear Malformation and Renal Anomalies

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LIST OF ABREVIATIONS, SYMBOLS AND ACRONYMS

APPD	Anteroposterior pelvis diameter
BOR	Branchio-oto-renal
CAKUT	Congenital anomalies of the kidney and urinary tract
CT	Computed tomography
IVU	Intravenous urography
KUB	Kidney, ureter and bladder
MCA	Multiple congenital anomalies
MCDK	Multicystic dysplastic kidney
MCUG	Micturating cystourethrogram
MRU	Magnetic resonance urography
PACS	Picture Archiving and Communication System
PUJ	Pelviureteric junction
PUV	Posterior ureteric valve
RIS	Radiology Information System
UTA	Urinary tract abnormality
VUR	Vesicoureteric reflux

ABSTRACT

Introduction. Congenital anomalies of renal and urinary tract and external ear malformation are both rare entity. There are multiple studies that concluded higher incidences of congenital renal anomalies in those with external ear malformation. Thus, this study was intended to determine the significance of the association between isolated external ear malformation and congenital renal anomalies.

Objective. To determine the association between isolated external ear malformation and congenital renal anomalies.

Methodology. Retrospectively, 125 subjects (study group) with sonography detected congenital anomalies of kidney and urinary tract (CAKUT) and 125 subjects with normal ultrasound kidney, ureter and bladder (KUB) (control group) were recruited from two centres; Hospital Tengku Ampuan Afzan (HTAA) and Hospital Universiti Sains Malaysia (HUSM). Images were reviewed using Picture Archiving and Communication systems (PACS). Presence of isolated external ear malformation i.e preauricular appendages, sinus and pinna abnormality were identified through either the case notes or the Radiology Information System (RIS).

Results. Urinary tract abnormalities with isolated external ear malformation were detected in 6 subjects. Five subjects with preauricular sinus have renal agenesis (2 subjects), vesicoureteric reflux (VUR) (1 subjects), renal duplex (1 subject) and ureterocoele (1 subject) respectively; and one subject with pinna abnormality had VUR. Pearson chi-square (X^2) test analysis proved non-significant association between these two groups ($p>0.05$).

Conclusions. There is a no significant association between isolated external ear malformation and congenital renal anomalies; hence routine ultrasound KUB is not

mandataory.

Keyword: CAKUT; external ear malformation; case-control

ABSTRAK

Pengenalan. Kecacatan kongenital buah pinggang dan kecacatan isolasi telinga luaran sangat jarang berlaku. Terdapat banyak kajian membuktikan mereka yang yang mempunyai kecacatan telinga luaran lebih berisiko untuk menghidapi kecacatan kongenital buah pinggang. Oleh yang demikian, perkara di atas dikaji untuk menyelidik signifikannya hubungkait di antara kecacatan isolasi telinga luaran dan kecacatan kongenital buah pinggang.

Objektif. Menentukan hubungkait antara kecacatan isolasi telinga luaran dan kecacatan kongenital buah pinggang.

Metodologi. Secara retrospektif, 125 kes yang menghidap kecacatan kongenital buah pinggang yang dikesan menggunakan pemeriksaan sonografi buah pinggang, ureter dan pundi kencing (KUB) dan 125 kes kawalan (pemeriksaan sonografi normal telah direkrut dari dua hospital; Hospital Tengku Ampuan Afzan (HTAA) dan Hospital Universiti Sains Malaysia (HUSM). Imej disemak dan diperiksa menggunakan *Picture Archiving and Communication Systems* (PACS). Manakala, pemeriksaan telinga seperti wujudnya lebihan kulit, sinus, dan kecacatan pinna melalui nota pesakit atau *Radiology Information System (RIS).*

Keputusan. Kecacatan kongenital buah pinggang pada pesakit yang mempunyai kecacatan isolasi telinga luaran telah dikesan seramai 6 orang. Lima kes yang mempunyai masalah *pit* / sinus di luar telinga menghidapi masalah refluks air kencing dari pundi kencing (1 subjek), satu buah pinggang (2 subjek) , system buah pinggang yang duplikasi (1 subjek) dan *ureterocoele* (1 subjek); dan manakala satu kes yang mempunyai masalah kecacatan pinna telah menghidapi masalah refluks air kencing (1 subjek). Analysis statistic *Pearson chi-square* (X^2) membuktikan tidak

ada hubungkait yang signifikan antara kecacatan isolasi telinga luaran dan kecacatan kongenital buah pinggang ($p>0.05$).

Kesimpulan: Hubungkait antara kecacatan telinga yang isolasi dan kecacatan buah pinggang yang kongenital adalah tidak wujud. Oleh yang demikian, pemeriksaan sonografi KUB adalah tidak mandatory.

Kata kunci: CAKUT; kecacatan telingan luaran; kes-kawalan.

1 INTRODUCTION

Congenital anomalies of the kidney and urinary tract (CAKUT) (Stoll *et al.*, 2014) are a spectrum of congenital abnormalities ranging from the absence of one kidney, dysplastic kidney and reflux problem within the urinary system. It can be sporadic or familial; syndromic or non syndromic; however, non-syndromic CAKUT is more common (Sahay, 2013). According to Sahay (2013), CAKUT is the most common anomalies detected antenatally, which is approximately 30% of all fetal anomalies and is the commonest etiology for the end stage renal failure in children. According to Stahl *et al.* (2006) and Sahay (2013) genetic mutations i.e. ROBO2 gene and PAX2 gene dictate the embryology of the kidney and urinary tract system leading to congenital abnormalities of kidney and urinary tract (Sahay, 2013).

Minor or isolated external ear malformation is found in 4-10 per 1000 population. There are several types of external ear malformation such as preauricular sinus, preauricular appendage, pinna abnormality and external canal atresia. The commonest being detected is pre-auricular skin tag (Patil, 2001). Preauricular tag, preauricular sinus and pinna abnormality are the abnormalities that are of higher risk of developing congenital anomalies (Wang *et al.*, 2001) (Kohelet and Arbel, 2000).

Embryologically, both systems rose from different tissue origin; the external ear arises from pharyngeal cleft (Patil, 2001) and the kidney arises from intermediate mesoderm (Kolbe *et al.*, 2014). Urinary tract formation

begins at 4th weeks of gestation and continued with nephrogenesis in the renal cortices until 34th to 36th weeks of gestation (Cuckow *et al.*, 2001). Development of external ear begins at gestational age of 40 to 45 days; and completed its formation at 4th month of gestation (Kosling *et al.*, 2009). The auricular abnormalities include the abnormality in its shape, presence of auricular appendages, anotia, microtia and preauricular sinuses. Small ear (microtia) can be familial with autosomal dominance (Patil, 2001). According to Moore and Persaud (1998), auricular appendages developed from the accessory auricular hillocks; affecting 1.5% of the population (Lizama *et al.*, 2007; Patil, 2001). Preauricular sinus is defined as blind-ending narrow tubes or pits. Embryologically, the basis is still unknown and some authors speculated it is due to failure of closure of the dorsal part of the first pharyngeal groove (Moore and Persaud, 1998). Its true incidence is unknown. It affects 10% of African population (Huang *et al.*, 2007). It also affects 10% of oriental races (Leung and Robson, 1992) with autosomal dominance inheritance. According to Scheinfeld *et al.* (2004) inheritance up to 25 to 50% of cases; but sometimes occur sporadically and may be associated with hereditary deafness (Patil, 2001).

Historically, Edith Potter associated the crumpled flattened ears with absence of bilateral kidney in 1946 (Wang *et al.*, 2001). Hilson (1957) first stated that a patient with external ear anomaly has higher incidence of having congenital anomalies in the kidney. Multiple studies have shown varieties of outcome. A study relating ear malformation and renal anomalies (Wang *et al.*, 2001) has shown significant incidence between isolated external ear

malformation and congenital renal anomalies, hence suggesting for routine imaging screening. Kohelet and Arbel (2000) stated that prevalence of renal abnormalities is higher in those with preauricular tag compared to the control group i.e. general population with no preauricular tag; and recommended urinary tract ultrasonography on all infants with isolated preauricular tags. Meanwhile, Kugelman *et al.* (2002) demonstrated that urinary tract anomalies are not associated with isolated preauricular tags and pits and that renal ultrasonography is not routinely recommended in these infants. The discordance finding from different studies may be contributed by few factors which include; 1) study conducted in patients with syndromes by genetic clinic which revealed higher incidence, 2) small sample size due to rarity of its incidence, and 3) study that has different time frame examination between case group and controlled group. These differences have raised the inquisition whether there are true association or not between the two, rendering the rise of controversy for routine screening ultrasound in all patient.

Ultrasound KUB has been modality of choices in screening in infants with isolated external ear malformation. This is because it is readily available, cheep and does not utilize ionizing radiation. As we all know, ultrasound examination is an operator dependent, hence only experienced and skilled operator are able to depict and demonstrate congenital anomalies. The sensitivity and specificity in diagnosing CAKUT is 95.7% and 66.7% respectively (Halim *et al.*, 2014). Having said that, in certain cases, whereby the primary sign such as refluxing urine in the distal ureter during micturition; in which is considered as 100% specific in case of vesicoureteric reflux; is not

visualized, having a secondary sign of dilated anterior posterior diameter of renal pelvis will prompt confirmatory investigation i.e micturating cysturethrogram (MCUG) to confirm the diagnosis. For such cases whereby diagnosis is not established during sonographic examination, ultrasound serve only as a screening tool for primary survey.

The practice in our center had encountered many requests for ultrasound kidney ureter and bladder (KUB) for an infant or child with isolated external ear malformation, even though they are of asymptomatic of any urinary tract disease. From our gross observation, many cases turned out to demonstrating normal sonographic study. On top of that, conflicting study from different literature made us inquisitive of relationship between isolated external ear malformation and congenital renal anomalies; hence questioning the need for routine ultrasound. Thus, this research was conducted to assess the relationship between isolated ear malformation and renal anomalies as well as to assess the yield of routine ultrasound KUB in our population and furthermore to determine the necessity for routine imaging.

2 LITERATURE REVIEW

2.1 Embryology of the Urinary Tract System and its congenital Anomalies

2.1.1 Embryology of Urinary Tract System

Moore and Persaud (1998) explained that there two components involved in the formation of urogenital tract; first, the collecting system and second, the excretory system and it begins its formation at fifth week after conception while its function begin after ninth week of conception. Collecting system derived from metanephric blastema, which is part of nephrogenic cord and excretory component derived from metanephrogenic diverticulum, which arise from mesonephric duct (Cuckow *et al.*, 2001; Moore and Persaud, 1998). It begins with the posterior-medial aspect of caudal part of mesonephric duct; near its entrance to the cloaca sprout a budding to form metanephric diverticulum or ureteric bud (Cuckow *et al.*, 2001; Moore and Persaud, 1998). This ureteric bud will penetrate with metanephric blastema (mass of mesenchyme) tissue and its bifurcates *(Sahay, 2013)* and called ampulla (Moore and Persaud, 1998; Sahay, 2013). Williams (2007) explained that each of this ampulla acquire a caplike aggregate of metanephric blastema tissue. And when the ureteric bud first comes in contact with the metanephric blastema, its tip expands and forming initial ampulla in which this initial ampulla forms renal pelvis (Moore and Persaud, 1998). At 6^{th} weeks ureteric bud bifurcates four times, result in four generations of bifurcation that give rise to 16 branches ureteric bud which will coalesce and form majox calyx *(Moore and Persaud, 1998; Sahay, 2013)*. At 7^{th} week of gestation, the next four

generations also coalesce and form minor calyx (Cuckow *et al.*, 2001). This further bifurcation results in fetal lobulation, which disappear during infancy. At the same time, formation of nephrons take place by undergoing epithelia conversion to form collecting system such as Bowman's capsule (Cuckow *et al.*, 2001). Moore and Persaud (1998) mentioned that the metanephric blastema tissue at the distal ends of ureteric bud differentiate into small vesicle namely metanephric vesicle. This metanephric vesicle will expand and form Bowman's capsule (Moore and Persaud, 1998) and it attains tuft of capillaries by invagination hence formation of glomerulus (Cuckow *et al.*, 2001; Moore and Persaud, 1998). Then the developed metanephric vesicles and ureteric bud will fuse to become one uriniferous tubules and later on it will elongate to form a complete nephron unit (Moore and Persaud, 1998). Between sixth until ninth week of gestation, the embryonic kidney change its position by ascension and attains into adult position at ninth week of gestation (Cuckow *et al.*, 2001; Moore and Persaud, 1998). As it ascend the kidney faces anteriorly and rotates medially hence anteromedial position of renal hilum (Cuckow *et al.*, 2001) and it receives its vascular supply from aorta (Williams, 2007).

Formation of urinary bladder begins with partitioning of the cloaca at approximately 4 weeks of gestation. It is partitioned by an ingrowth of mesoderm from the point of confluence of the allantois and the hindgut forms a septum namely urorectal septum and progressively this septum grow until it reaches the cloacal membrane (Cuckow *et al.*, 2001). These septum separate between urogenital sinus and rectum and cloacal membrane is also divided

into anterior urogenital membrane and posterior anal membrane (Moore and Persaud, 1998). As the bladder enlarge, the mesonephric ducts distal in which the ureteric bud sprout out from incorporated into the posterior aspect of the primitive urogenital sinus progressively and similarly ureteric orifices also blends the posterior wall of the developing bladder, hence separation with the mesonephric duct orifices (Cuckow *et al.*, 2001)

At the 7th weeks of gestation, the urogenital membrane disintegrates and forms a communication between the urinary tract and the amniotic cavity (Cuckow *et al.*, 2001). Moore and Persaud (1998) described then the urogenital sinus is divided into a vesical part (cranial) that continuous with the allantois, pelvic part which later on develops to form the urethra in the bladder neck and phallic part (caudal) that grows toward the genital tubercle. Later on, the mesonephric ducts from the primitive urogenital sinus fuse in the midline forming a triangular area between them two ureteric orifices that is known as trigone (Cuckow *et al.*, 2001; Moore and Persaud, 1998). The allantois that is in continuity with the vesical part of urogenital sinus becomes constricted and fibroses, called urachus (Moore and Persaud, 1998). Finally, the fate of mesonephric duct are absorbed and the ureters enter separately at the base of urinary bladder (Moore and Persaud, 1998).

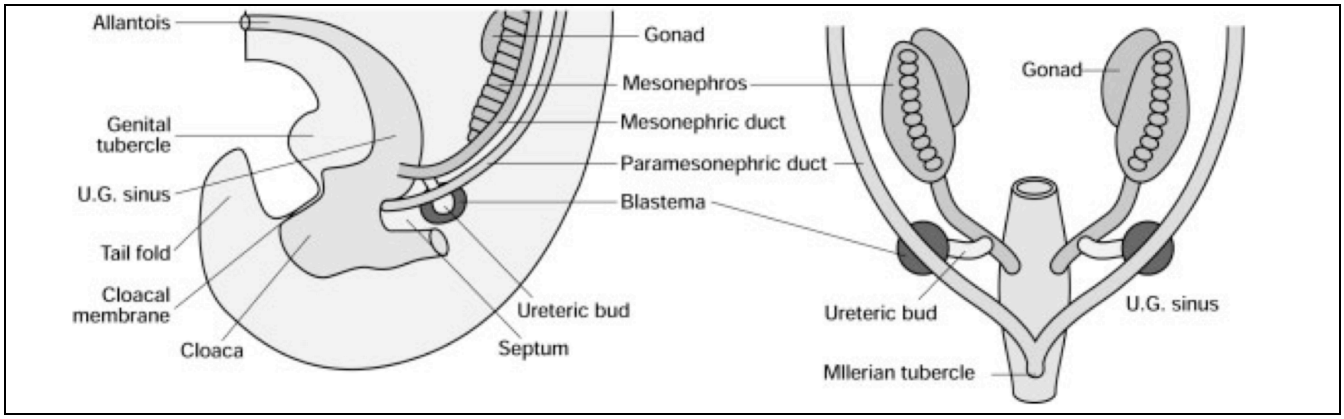


Figure 1: Schematic diagram of embryological process of urogenital tract at fifth week of gestation. Image showed mesonephric duct; near its entrance to the cloaca sprout a budding to form metanephric diverticulum or ureteric bud.

Source (Cuckow *et al.*, 2001)

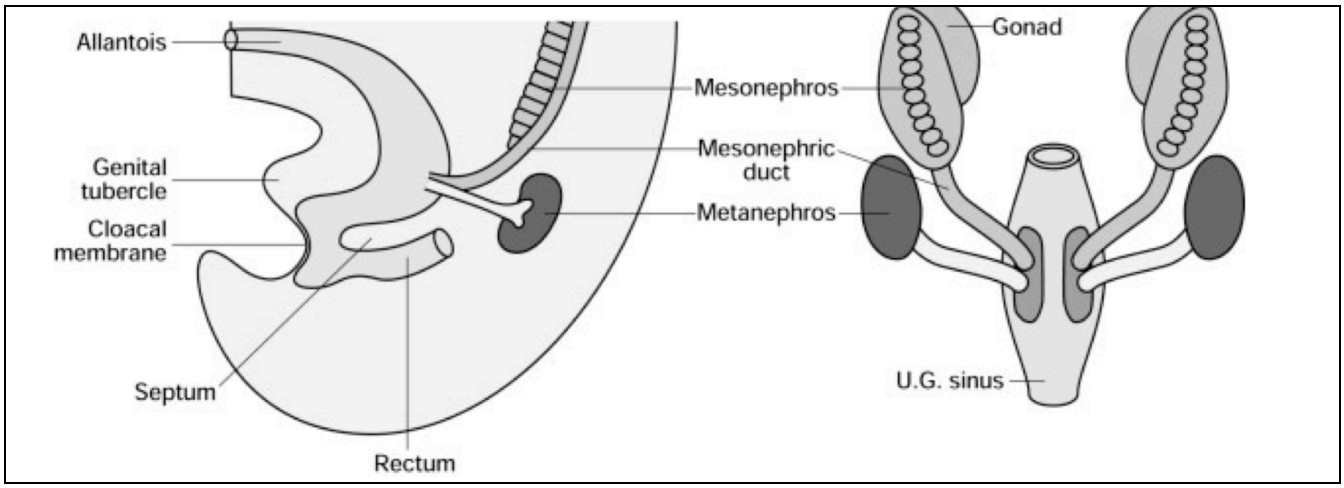


Figure 2: Schematic diagram of embryological process of urogenital tract at sixth week of gestation. Ureteric bud first comes in contact with a caplike aggregate of metanephric blastema (from metanephros) tissue. Source (Cuckow *et al.*, 2001)

2.1.2 Radiological Investigation for Congenital Anomalies of Urinary Tract

Ultrasound is the commonest imaging technique requested in paediatric age group to screen or diagnose renal pathology, be it congenital or acquired (Berrocal et al., 2002; Mercado-Deane et al., 2002). It is preferred as it is readily available, cheap and a non-ionizing radiation utility. The indications are patient with history of urinary tract infection; especially recurrent event, renal dysfunction and to exclude structural abnormalities (Williams, 2007). In case of newborns, other indications are also included i.e. antenatal history of oligohydramnios whereby ultrasonography is advised within the first 24 hours after delivery (Sahay, 2013). In a prenatal diagnosis of hydronephrosis, ureterocele, thickened bladder, renal cysts, or increased echogenicity renal parenchyma; sonographic reassessment should be expedited within 48hours of life. However, dilated collecting system might be missed during that duration due to newborn's state of volume-contraction (Sahay, 2013). Halim *et al.* (2014) investigated the diagnostic accuracy of transabdominal ultrasonography in correlation with intravenous urography (IVU) in suspected patients of congenital anomalies of kidney and ureter and demonstrated sensitivity was of 95.7%, specificity was of 66.7%, positive predictive value was of 97.8%, negative predictive value was of 50.0% and accuracy was 94.0%.

Micturating cystourethrography (MCUG) is indicated in those patients with collecting system dilatation and suspected vesicoureteric reflux (VUR) (Berrocal *et al.*, 2002; Sahay, 2013). Intravenous urography is advocated to

specifically identify area of obstruction and its affected level, diagnose ureterocele and determine presence of duplex system (Berrocal et al., 2002). Renal scintigraphy is helpful to differentiatiate between obstructed and non-obstructed mega ureter (Berrocal *et al.*, 2002; Sahay, 2013). Magnetic resonance urography is useful to demonstrated ectopic extravesical ureteric insertions (Berrocal et al., 2002).

2.1.3 CAKUTS

Congenital anomalies of the kidney and urinary tract (CAKUT) (Stoll *et al.*, 2014) are a spectrum of congenital abnormalities ranging from the absence of one kidney, dysplastic kidney and reflux problem within the urinary system. It can be sporadic or familial; syndromic or non syndromic; nonsyndromic CAKUT is more common (Sahay, 2013).

According to Sahay (2013), CAKUT is the commonest anomalies detected antenatally approximately 30% of all anomalies; with prevalence of 1 in 500 fetal sonographic study. Patient can be asymptomatic; however, according to Stahl *et al.* (2006) and Sahay (2013) CAKUT is the commonest etiology for the end stage renal failure in children. Genetic mutations dictate the embryology of the kidney and urinary tract system leading to congenital abnormalities of kidney and urinary tract (Sahay, 2013). Patient with CAKUT may present with hypertension, proteinuria and sometime abdominal mass resulting from gross hydronephrosis or dysplastic kidney (Sahay, 2013). On top of that, child with obstructive outflow obstruction may present with pelvic

mass due to hypertrophic urinary bladder and CAKUT causes 30% to 50% of cases of end stage renal disease in children (Sahay, 2013).

2.1.3.1 Abnormality of the Kidney

Agenesis of the kidney occur between fifth week to seventh week due to failure of ureteric bud formation from the mesonephric duct, hence failure of metanepheric differentiation induction (Siegel, 2002). Bilateral renal agenesis are very rare and it occurs in 1 per 3000 to 10,000 births (Sahay, 2013) in which patient died because lung hypoplasia and respiratory distress *(Williams, 2007).* Sonographically*,* it is characterized by empty renal fossa, absence renal artery and ipsilateral adrenal gland will be flattened (Figure 3) and elongated due to absence of conforming effect from the kidney contour (Mercado-Deane et al., 2002). The contralateral normal kidney will be hypertrophied within sixth to twelfth months of life (Siegel, 2002) and patient is usually assymptomatic (Sahay, 2013). Renal agenesis is associated with VUR by 37% (Sahay, 2013; Williams, 2007), pelviureteric obstruction junction and ureterovesical junction obstruction by 10-15% (Sahay, 2013). Meanwhile, if the kidney is small as the renal length measures of less that 2 SD below the mean for age; it is considered as hypoplasia (Sahay, 2013). Ultrasound features in hypoplasia includes, present but small kidney with contralateral hypertrophied kidney (Siegel, 2002).

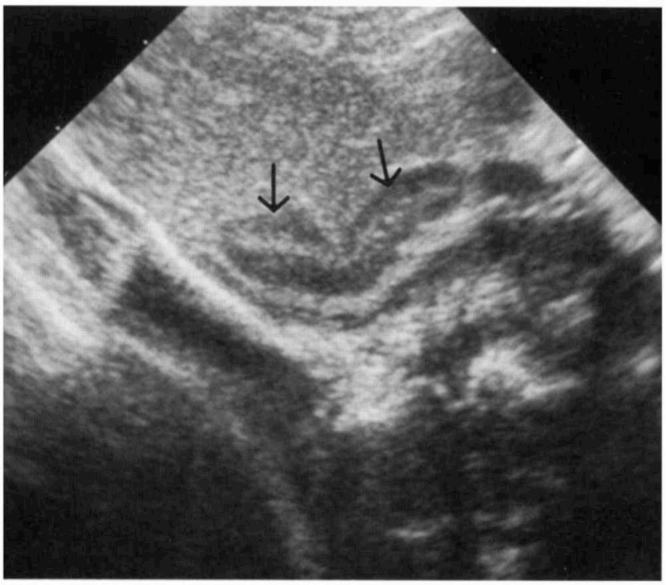
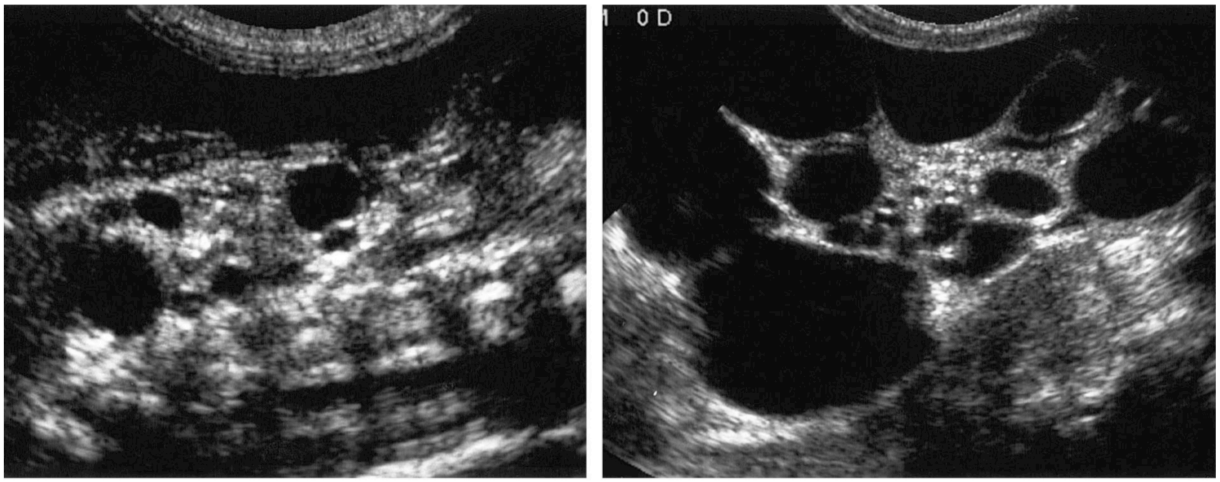


Figure 3: Ultrasound finding of elongated ipsilateral adrenal glands (arrow) in the absence of kidney. Source: (Siegel, 2002)

The second commonest cause of abdominal distension in neonate is multicystic dysplastic kidney (MCDK) *(Mercado-Deane et al., 2002)* and it is the commonest form of renal cystic disease (Kolbe *et al.*, 2014). It is sporadic (Kolbe *et al.*, 2014) with incidence of 1 in 3000 (Sahay, 2013) and associated with VUR by 10-20% (Mercado-Deane *et al.*, 2002) and contralateral ureteropelvic junction obstruction (Kolbe *et al.*, 2014). Sonographically (Figure 4), finding is of a mass of multiple noncommunicating cysts of variable size (Mercado-Deane et al., 2002) with minimal to no normal renal parenchyma intervening between the cyst (Kolbe *et al.*, 2014).



(a) (b)

Figure 4: Ultrasound finding demonstrate multiple renal cysts of varying sizes in two different patients (a) and (b) with no normal renal parenchyma intervening within.

Source: (Mercado-Deane et al., 2002)

Failure in kidney migration has lead to the ectopic location of kidney (Sahay, 2013; Williams, 2007) and the is found as per 1 case in 1000 autopsied body and 1 in 10000 patient in clinical setting with no gender predilection (Sahay, 2013). William (2007) mentioned that patient is usually asymptomatic; if not, patient presented with urinary tract infection. Unilateral renal ectopia is common with left sided predilection and bilateral renal ectopic occurs in 10% of cases (Sahay, 2013). Siegel (2002) described renal ectopia as simple (which is also known as pelvic kidney) or crossed renal ectopia. Simple ectopia refers to kidney fail to ascend and remain at expected side of the spine meanwhile; cross ectopia refers when the ectopic kidney cross midline. Simple ectopia usually located at lower sacral posterior to the urinary bladder or anywhere along migration pathway until renal fossa (Mann, 2011).

According to Sahay (2013), cross ectopia may fuse to the contralateral kidney; fused cross ectopia occurs in 90% of cases (Siegel, 2002). Cross renal ectopic is more common in boys (Mann, 2011). Ultrasound features of Scintigraphy study often demonstrate reduced in function (Sahay, 2013).

The commonest type of fusion anomaly is horseshoe kidney (Palmer, 2013; Siegel, 2002) with incidence of one in 400 to 800 live births (Mann, 2011). It fuses at its inferior pole, while the isthmus (fused renal tissue) may be composed of normal renal parenchyma or fibrous tissue (commoner) (Sahay, 2013). Assessment of functionality of the isthmus can be both demonstrated by ultrasound and ^{99m}Tc-dimercaptosuccinic acid (^{99m}Tc-DMSA scan) (Mann, 2011) (Figure 5). Fused kidney remains in the pelvis or at the level of L4 to L5. (Sahay, 2013). Fusion of the inferior poles of bilaterally kidney and malrotation of renal hilum are typical horseshoe kidney appearance and increased uptakes in the isthmus (Figure 2.1.4.1(iii)) during ^{99m}Tc-DMSA study represent functioning tissue (Mann, 2011). Patient with horseshoe kidney is at risk of Wilm's tumor which can be detected by ultrasound (Palmer, 2013).

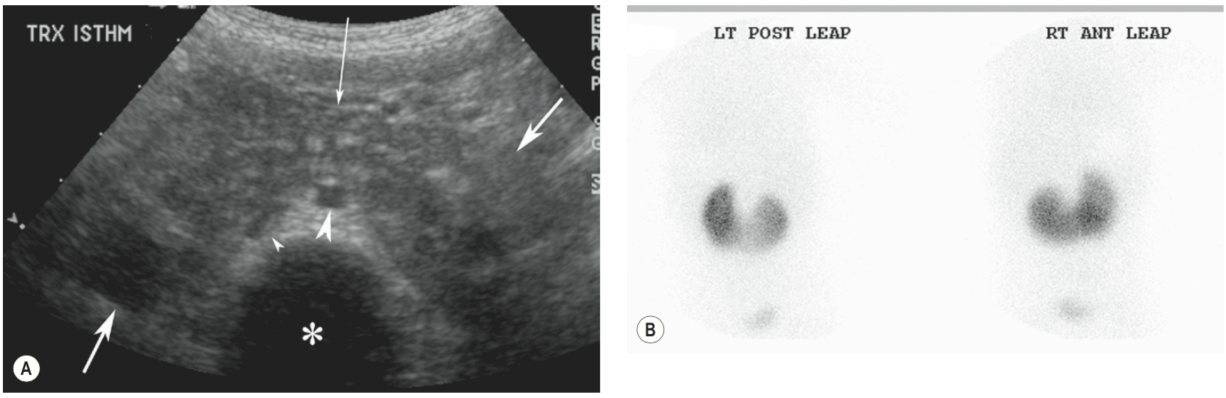


Figure 5: Sonographic image represent horseshoe kidney (two solid arrows on the right and left) with isthmus (long arrow) that made of normal renal parenchyma. Isthmus of the horseshoe kidney is in the proximity of the inferior vena cavae (small arrow head) and abdominal aorta (large arrow head). Static renal scintigraphy demonstrate isthmus in made of functioning renal parenchyma tissue.

Source: (Mann, 2011)

2.1.3.2 Abnormality of the Collecting system

Duplication is the commonest anomaly of the upper renal collecting system and is found most often in girls (Meyers and Epelman, 2011). There are two types of renal duplications namely incomplete and complete. The former are more common and account for more than 95% of the duplication anomalies (Siegel, 2002). The incidences are 0.8 – 5% (Williams, 2007). Incomplete duplication has spectrum of a bifid infundibulum to duplicated ureters (Dillman and Bates, 2014) whereby the ureter fused at any level before entering the urinary bladder (Siegel, 2002). It also can occur involving uni- or bilateral kidney (Meyers and Epelman, 2011). According to Weigert-Meyer rule, it explains the "ureter that drain the upper moiety inserts inferior and medial to the lower moiety ureter" (Dillman and Bates, 2014); hence upper moiety is commonly obstructed presented as hydronephrosis and occasionally hydroureter and ureterocele too (Meyers and Epelman, 2011). In incomplete duplication, child usually asymptomatic; whereas, in complete duplication, sepsis is a presentation as infection sets in obstructed upper pole moiety is (Dillman and Bates, 2014) or stagnant urine of VUR of the lower moiety system (Meyers and Epelman, 2011). Ultrasound usually demonstrates two central echogenic foci that are divided by a normal renal parenchyma (Palmer, 2013) (Siegel, 2002). In case of non-obstructive duplicated kidney, there will be unilateral kidney enlargement (Siegel, 2002). MCUG commonly employed to demonstrate VUR (Palmer, 2013). MRU using

T2 weighted imaging capable to precisely outline the duplicated system (Dillman and Bates, 2014).

Ureterocoele is a congenital abnormality that is characterised by the presence of saccular, submucosal intravesical portion of ureteric dilatation (Mann, 2011). There is female preponderance and usually seen in relation to a duplex kidney by 75% (Mann, 2011). Cases can be diagnosed prenatally and 90% of the ureterocoeles are detected by the age of 3 (Riccabona and Bates, 2014). There are two subtypes which 1) intravesical ureterocoele - (referring to normal ureteric insertion) which is accounts for 20% of case, usually unilateral (Mann, 2011) and more commonly found in adult; and 2) ectopic ureterocoele - (referring to abnormal ureteric insertion) - more in children and is five to seven times more frequent in females (Riccabona and Bates, 2014). Patient usually presented with complication such as infection, secondary renal calculi and obstructive uropathy (Mann, 2011). Sonographically, features include a round thin walled lesion at the bladder base associated with dilated ureter (Palmer, 2013 & (Mann, 2011). It can be septated or multiloculated (Dillman and Bates, 2014). MCUG is best reviewed during early filling because as the urinary bladder filled with contrast, ureterocoele will be compressed or flattened against its wall hence false negative. In a true positive case, MCUG will demonstrates radiolucent filling defect within the urinary bladder and MRU demonstrates ‘cyst in cyst’ appearance in sequence of contrast-enhanced diuretic T1-weighted (Riccabona and Bates, 2014).

The most common cause of hydronephrosis in neonate is pelviureteric junction obstruction (Mercado-Deane *et al.*, 2002). The incidence is 3 in 1000 live births, with boys preponderance and left kidney predilection (Dillman and Bates, 2014). It can be bilateral by 30% of the cases (Dillman and Bates, 2014); though the severity of obstruction can be asymmetry (Dillman and Bates, 2014). It is thought to be due to replacement of smooth muscle by collagen or secondary cause due to bands, kinks, or aberrant vessel (Mercado-Deane *et al.*, 2002) & (Dillman and Bates, 2014). During neonate, it may be detected through antenatal checkup scan (Mercado-Deane *et al.*, 2002). Postnatally, infant may present with palpable abdominal mass, haematuria, infection or sometimes an incidental finding (Mercado-Deane *et al.*, 2002) (Dillman and Bates, 2014). As child grow, late detection leads to calculus formation, urosepsis and haemorrhage (Dillman and Bates, 2014). Some child suffers from renal failure (Mercado-Deane *et al.*, 2002). Occasionally, abdominal pain is triggered by sudden acute distension renal pelvis due to increased in fluid intake (Meyers and Epelman, 2011). Ultrasound basically reveals evidence of obstruction. It is characterised by pyelectasis with renal pelvic dilatation more than 10mm in diameter (Mann, 2011). Ureter distal to the obstruction is of normal caliber (Mercado-Deane *et al.*, 2002) ; (Dillman and Bates, 2014). Dynamic renal scintigraphy can be used to assess renal function and drainage (Dillman and Bates, 2014). MRU is helpful in assessing patient with complex anatomical especially when the location of the obstruction is not obvious from ultrasound finding (Tröger and Seidensticker, 2008).

2.1.3.3 Abnormality of the Urinary Bladder

Vesicoureteric reflux is due to reflux of urine from urinary bladder into the ureter due to failure of valvular mechanis in the ureterovesical junction (Tröger and Seidensticker, 2008). VUR is the commonest entity of CAKUT encountered with incidence of 1% to 5%. It can be primary and secondary. Primary VUR may be dominant or recessive with several of gene loci have been identified though which gene has not been ascertained (Berrocal et al., 2005). Primary VUR is commonly occur in girl, whereas, secondary VUR due to bladder outlet obstruction have boy predilection (Riccabona and Bates, 2014). Other congenital anomalies are associated with VUR by one-third (Sahay, 2013). Patient may present with urinary tract infection with primary VUR comprised of one third of cases (Berrocal et al., 2005). It also can be asymptomatic as it may resolve spontaneously as the patient grows older (Cuckow et al., 2001). In a child with urinary tract infection, 50% of patients have VUR (Donnelly, 2009). Complication includes reflux nephropathy in a patient with VUR complicated with infection. This accounts for 30%–50% of end-stage renal disease in pediatric cases and 20% of end-stage renal disease in adults (Berrocal et al., 2005). Tröger and Seidensticker (2008) mentioned that "When intermittent dilatation of the renal pelvis or different diameters of the renal pelvis before and after micturition are observed, think of VUR" and this finding specific for VUR. Mann (2011) stated that meticulous sonographic examination made diagnosis possible. Ultrasound is also used in follow up study (Palmer, 2013). MCUG is gold standard for diagnosing VUR; predominantly to assess posterior urethral

valve and grade the reflux. The grading of VUR is as diagram below:

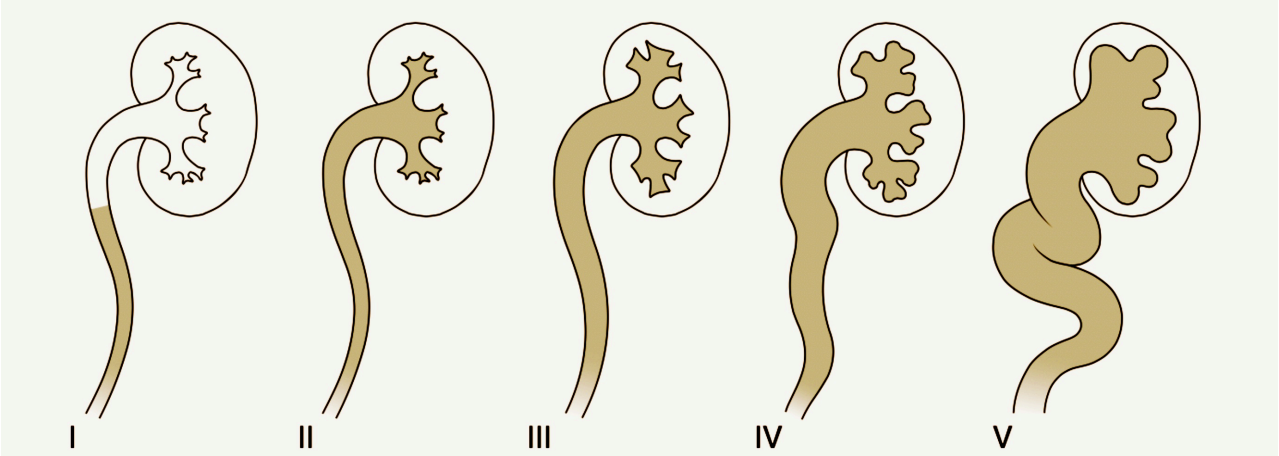


Figure 6: Grading of vesicoureteric reflux. Grade I: reflux limited to ureter; grade II: reflux up to renal pelvis; grade III: mild dilatation of ureter and pelvicalyceal system; grade IV: tortuous ureter with moderate dilatation, with blunting of fornices but preserved papillary impression; grade V: tortuous ureter with severe dilatation of ureter and pelvicalyceal system, loss of fornices and papillary impression.

Source: (Riccabona and Bates, 2014)

2.1.3.4 Abnormality of the Urethra

Posterior urethral valves (PUV) are currently is regarded as congenital obstructive posterior urethral membrane (Riccabona and Bates, 2014). It is a common anomaly of congenital urinary bladder outlet obstruction (Riccabona and Bates, 2014). It usually affected boys (Mercado-Deane *et al.*, 2002) and lesion is detected at first decade of life (Riccabona and Bates, 2014). US

reveals secondary finding such as bilateral hydronephrosis and hydroureter, thickened and trabeculated bladder wall (Mercado-Deane et al., 2002). Transperineal ultrasound occasionally demonstrate dilated prostatic urethra during micturition (Riccabona and Bates, 2014). The goal standard imaging is retrograde cystourethrography (Sahay, 2013). Primary finding is the visualization of actual valve and secondary findings include evidence of obstruction i.e. hydronephrosis, thickened and trabeculated urinary bladder wall (Riccabona and Bates, 2014)

2.2 Embryology of External Ear and its Congenital Anomalies

External ear is made of three components, which include pinna, external ear meatus and tympanic membrane (Moore and Persaud, 1998). For the purpose of the study, author will briefly discuss on the formation of pinna (auricle). According to Moore and Persaud (1998), pinna arise from ectoderm of first and second branchial arch. It begins at gestation age of 40 to 45 days; and completed is formation at 4th month of gestation (Kosling *et al.*, 2009). The auricle arises from a series of elevations termed 'auricular hillocks' around the first pharyngeal cleft (Patil, 2001). These auricles first appear at the base of neck, and as the mandible is formed; auricles ascend to their normal position, which is side of the head (Moore and Persaud, 1998)

There are vast ranges of external ear malformation. However, in this study author will discuss only few of the auricular abnormalities which include

abnormality in its shape i.e microtia and anotia, presence of auricular appendages, and preauricular sinuses.

Microtia (Figure 7) is a small ear, which is due to suppressed development of auricular hillocks; and anotia is absence of pinna is due to failure of auricular hillocks to develop at all (Moore and Persaud, 1998). Meanwhile; “Microtia-anotia is defined as deformed or absent pinna with an atretic ear canal” (Patil, 2001) and it associated with conductive hearing loss. Microtia-anotia can be familial with autosomal dominance and sometimes multifactorial; however, mere anotia is associated with ipsilateral facial paralysis and absence of tonsil (Patil, 2001).

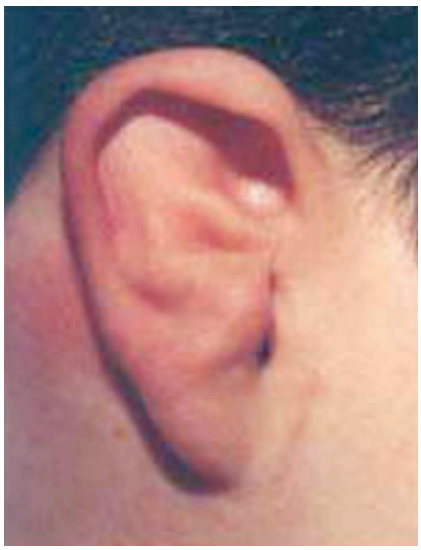


Figure 7: Microtia. Small ear with deformed ear lobe and abscence tragus. Source: (Bent, 2011).

According to Moore and Persaud (1998), auricular appendages (Figure 8) developed from the accessory auricular hillocks; and it commonly unilateral, located anterior to the auricle and it can be sessile or pedunculated in shape. It is common affecting 1.5% of the population (Lizama *et al.*, 2007; Patil, 2001).

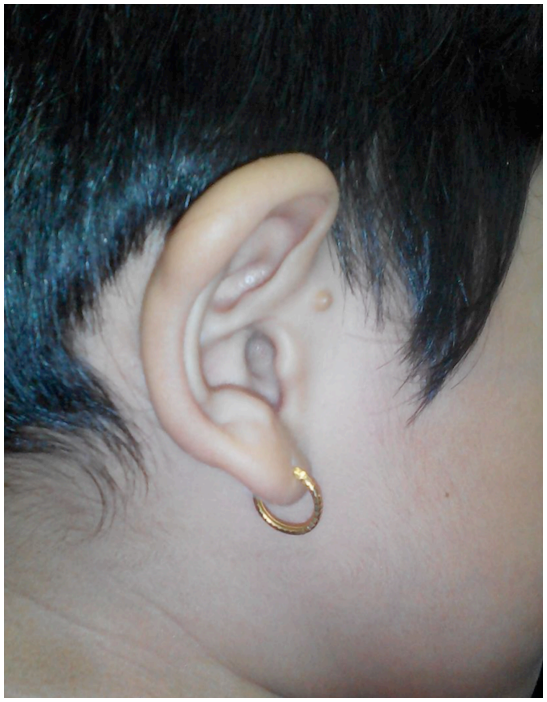


Figure 8: Preauricular appendages (sessile).

Next, is preauricular sinus, which according to Patil (2001) defined as blind-ending narrow tubes or pits (Figure 9). Though it is harmless, it can get infected due to retention cysts or chronic discharge. Embryologically, the basis is still unknown and some speculate due to failure of closure of the dorsal part of first pharyngeal groove (Moore and Persaud, 1998). Its true incidence is unknown; it affects 10% of African population (Huang *et al.*, 2007) and 10% of oriental races (Leung and Robson, 1992). It affects 0.9% of

Europe population; with autosomal dominance inheritance and according to Scheinfeld *et al.* (2004) inheritance up to 25 to 50% of cases; but sometimes occur sporadically and may associated with hereditary deafness (Patil, 2001).

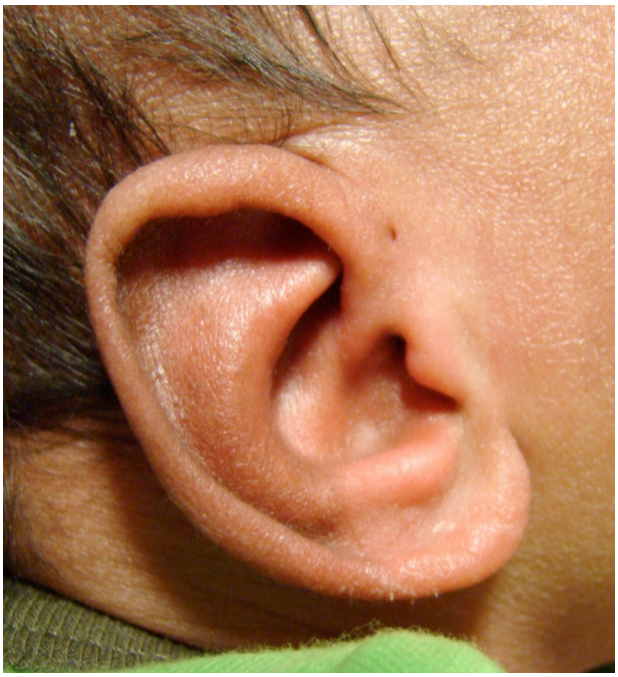


Figure 9: Preauricular sinus. Small pit anterior to auricle.

Source: (Stulberg, 2014)

2.3 Relationship between Isolated External Ear Malformation and Renal Anomalies

In 1946, Edith Potter associated the crumpled flattened ears with absence of bilateral kidney (Wang *et al.*, 2001). Hilson (1957) first stated that a patient with external ear anomaly has higher incidence of having congenital anomalies in the kidney. Wang *et al.* (2001) conducted a study in a total of 42 patients with ear anomalies whom received renal ultrasound; 12 (29%) of them displayed renal anomalies. It is concluded that there is associated