

Harnessing the Physical Examination for the Early Detection of Congenital Anomalies of the Kidney and Genitourinary Tract

Kamal Akl^{1}*

Abstract

Congenital anomalies of the kidney and urinary tract are the major cause of end stage renal failure in childhood.

Methods: literature search was done via Pubmed looking for use of the physical examination for the early detection of congenital anomalies of the kidney and urinary tract.

Results: Few papers emphasized using the physical examination for the diagnosis of congenital renal anomalies.

Conclusion: Physical examination clues may help in the early diagnosis of congenital anomalies of the kidney and urinary tract, especially in developing countries where genetic testing is expensive and not readily available.

Keywords: Congenital, Kidney, Examination.

(J Med J 2016; Vol. 50 (4): 203-208)

Received

Aug. 1, 2016

Accepted

Sept. 25, 2016

Introduction:

While Congenital anomalies of the kidney and urinary tract(CAKUT) are the major cause of end stage renal failure(ESRF) in childhood,¹ many cases remain undiagnosed, only to present as proteinuria, hypertension, and ESRF in young adults.²

Early diagnosis is important to avoid morbidity and mortality. The pediatrician is usually the first person to encounter such patients. However, the diagnosis is frequently missed even by the nephrologist , since key physical examination findings are often overlooked. There are few papers in the

literature that mention the association of extrarenal manifestations with occult nephro-urological findings.⁴⁻⁶

The purpose of this paper is to search the literature for papers emphasizing physical examination clues that might lead to early diagnosis and treatment of CAKUT.

Methods: Literature search was done via the electronic data base pubmed for 40 years last accessed in may 2015 looking for papers that emphasized the importance of the physical examination in the early diagnosis of CAKUT. Search was done using the terms CAKUT, renal dysplasia, and individual diseases or

1. Professor of Pediatrics, Consultant Pediatric Nephrologist, Department of Pediatrics, Jordan University Hospital and School of Medicine, The University of Jordan, Amman, Jordan.

* Correspondence should be addressed to:

Kamal Akl; Professor of Pediatrics, Consultant Pediatric Nephrologist, Department of Pediatrics, Jordan University Hospital and School of Medicine, The University of Jordan, Amman, Jordan.

P. O. Box: 13046 Amman 11942, Jordan.

E-mail: kachbl@yahoo.com

© 2016 DAR Publishers / The University of Jordan. All Rights Reserved.

syndromes. CAKUT is defined as renal dysplasia \pm vesicoureteral reflux (VUR) with and without obstructive uropathy.⁷ Renal dysplasia is disorganized kidney development, and renal hypoplasia is decreased number of normal nephrons, associated with small kidneys.

Results: Literature search yielded few papers emphasizing use of the physical examination for the diagnosis of individual diseases rather than CAKUT as a whole. Selected results were shown in table.⁸⁻²⁰ Use of the physical examination disclosed the following clues:

Minor anomalies: such as the grimace when smiling in the urofacial syndrome. A clue that may easily be missed, except with previous knowledge of the existence of the syndrome or in the presence of a positive family history.

Major anomalies: Many of the syndromes listed in the table had obvious phenotypic abnormalities that were hard to miss. However, when part of the syndrome existed in isolation, a high index of suspicion and follow up yielded the correct diagnosis. Cases of prune belly syndrome with hydronephrosis in the presence of partial absence of the abdominal muscles were easily missed at initial visits.

Discussion

The clinical presentation of CAKUT is very heterogeneous with diverse clinical phenotypes.^{3,21} In 2006 The British Association of Pediatric Nephrology (BAPN) redefined CAKUT as renal dysplasia \pm VUR with and without obstructive uropathy.⁷

CAKUT phenotypes include renal

hypoplasia, dysplasia, agenesis, multicystic dysplastic kidney (MCDK), collecting system (hydronephrosis, peviureteric junction obstruction, and megaureter), ureterocele, vesicoureteral reflux (VUR), and posterior urethral valves (PUV). Nonobstructive renal dysplasia may be syndromic or nonsyndromic. While VUR is common, bilateral renal agenesis is rare.¹⁵ The end result of CAKUT is ESRF via the mechanism of hyperfiltration in the remnant nephrons.

Soliman and associates from Egypt conducted a prospective study on 107 children with the diagnosis of CAKUT. Familial clustering was identified in 14% of the cohort. Syndromic CAKUT accounted for 31.8%, and posterior urethral valve 36.4%. End stage renal disease was found in 9.3% of the cohort at presentation. PUV was found in 60%. Renal damage was more obvious in the obstructive cases compared to the nonobstructive ones.²¹

In a cross-sectional study of all antenatal CAKUT cases in Saudi Arabia, the types of CAKUT were hydronephrosis 51.1%, renal agenesis 8.5%, MCDK 12.8%, polycystic kidney disease (PCKD) 17.7%, PUV 2.13%, and prune belly syndrome (PBS) 0.71%.

Bondagii reported a higher prevalence, but similar pattern of distribution of CAKUT in Saudi Arabia than in developed countries.²²

Hwang et al. analyzed a cohort of 749 individuals from 650 families with CAKUT. The most common phenotypes in this CAKUT cohort were VUR in 288 patients, renal hypodysplasia in 120 patients, and unilateral renal agenesis in 90 patients.²³

A common genetic background with variable penetrance seems to play a role in the development of the wide spectrum of CAKUT

phenotypes. While many cases of CAKUT are sporadic, familial cases point towards a genetic basis.^{21,23-26} especially in populations with a

high rate of consanguinity such as the Middle East.²⁸

Table 1. Physical examination clues in various presentations of nephro-urologic disorders

Presentation	check	Clue	Diagnosis	Other findings	Ref
ESRF	Eyes	Coloboma	Charge syndrome	Choanal stenosis/atresia;developmentaldelay; abnormal ear shape	8
	Eyes	Coloboma	RCS	oligomeganephronia; MCDK;VUR	9
	Eyes	Aniridia	WAGR syndrome	Wilmstumor; genitourinary abnormalities; mental retardation	10
	Ears	Preauricular pits/tags	BOR syndrome	Hypoplastickidneys;hearing loss; absence of pinna; cervical fistulae	11
	Digits	Complete syndactyly; fusion of ulna and radius	Cenani Lenz syndrome	Renal agenesis; ectopic kidney	12
	Digits	Polydactyly	BBS	Mental retardation; hypogenitalism; Renal dysplasia; central obesity; retinal dystrophy	13
Proteinuria	Digits	Absence of middle finger; lobster hands	Acrorenal syndrome	Renal hypodysplasia	14
Hypertension	Digits	Brachydactyly	Hypertension Brachydactyly syndrome	Brachydactyly appears after puberty; liable to fatal strokes between 40-50 years	15,16
Voiding dysfunction	Mouth	Grimace when smiling	Urofacial syndrome	Uropathy; hydronephrosis; neurogenic bladder; UTI	17
	Abdomen	Partial/complete absence of abdominal muscles	Prune Belly Syndrome	Hydroureteronephrosis ; VUR; cryptorchidism	18
	Nose	Bifid	BNAR syndrome	Renal agenesis; ARM	19,20

ESRF: End stage renal failure; RCS: Renal coloboma syndrome; MCDK: Multicystic dysplastic kidney; VUR: Vesicoureteral reflux; WAGR: Wilms tumoraniridia genitourinary abnormalities retardation; BOR: Brachiootorenal; BBS: bardetBiedel syndrome BNAR: Bifid nose anal anomalies renal dysplasia ARM: Anorectal malformations

Family history is important. A high frequency of kidney and urinary tract anomalies was found in asymptomatic first-degree relatives of patients with CAKUT.^(29,30) There is a 10% incidence of asymptomatic renal malformations in parents/siblings of index cases with bilateral renal agenesis. Syndromes have phenotypic and genetic heterogeneity. Relatives of a patient with

CAKUT may have an isolated renal anomaly, without the associated extra renal manifestations. Carriers of Bardet Beidelsyndrome sixteenth locus mutation present with absence of polydactyly and early ESRF.

Kohl and associates showed that biallelic missense mutations in the Fraser/Manitoba-

oculo-tricho-anal (MOTA)/ Bifid Nose Renal Agenesis and Anorectal malformations spectrum (BNAR) genes may cause isolated CAKUT. truncating mutations which manifest as the multiorgan form of Fraser syndrome.³¹ Epigenetics plays a role in the development of the phenotype. Delayed diagnosis results in adult presentation of CAKUT with hypertension, proteinuria, and ESRF of uncertain etiology.³ General pediatricians and nephrologists may follow patients with occult nephropathy without realizing that physical examination clues exist early in life. As shown in table , in a child with the urofacial syndrome early diagnosis of this hereditary syndrome may avoid the development of ESRF.¹⁷ Physical examination should be geared by antenatal ultrasonography, family history, and the presence of extrarenal anomalies. As an example, in the presence of family history of hypertension one should check for brachydactyly in adults and older children. Missing the Hypertension Brachydactyly Syndrome (HBS) may lead to fatal strokes at the ages of forty to fifty.¹⁵ Usually CAKUT is discovered by antenatal ultrasonography, during the radiologic investigation of urinary tract infection, and rarely by postnatal physical examination. The importance of family history cannot be overlooked. Important clues on antenatal ultrasound that may lead to the diagnosis of possible renal pathology include oligohydramnios, increased renal echogenicity, renal cysts, poor corticomedullary differentiation, non-visualized renal pyramids, cortical thinning, dilated bladder, multiple systemic malformations, ureteral and/or calyceal dilation, and duplex kidney. After the age of 6 months, hyperechoic kidneys reflect renal pathology in children.³² Antenatal detection of CAKUT helps in early diagnosis and management. However, despite routine

ultrasonography, antenatal diagnoses are frequently missed.⁷ The presence of extrarenal anomalies should alert the clinician to the possible existence of associated renal anomalies. In a systemic review Westland et al. found that one third of patients with unilateral renal agenesis had extrarenal anomalies.³³ In patients with preauricular pits and tags, 4-9% have an associated renal anomaly.

Ganesan et al. studied 122 patients with anorectal malformations (ARM) found out that urological anomalies existed in 23%. VUR, neurogenic bladder, and a single kidney were the most common anomalies. Significant factors for predicting the presence of urological anomalies included high ARM lesion, presence of a genital abnormality, and cloacal anomaly in girls. Patients with ARM may be at low risk of future renal failure. Risk factors included recurrent urinary tract infections (UTI) in 87%, neurogenic bladder 57%, and high grade vesicoureteral reflux in 87%, and single functioning kidney in 71%.³⁴ Physical exam clues may be present, long before kidney function deteriorates, thus providing an opportunity for delaying progression by use of angiotensin receptor antagonists/blockers. The presence of a solitary functioning kidney should alert the clinician to future development of hypertension, proteinuria and renal failure.^{3,30} Westland et al. recommend close follow up of patients with a solitary functioning kidney. Risk factors for deterioration included small renal size, prematurity, low birth weight, and history of urinary tract infections.³⁶

Conclusion:

CAKUT may be isolated and nonsyndromic, or exist as part of a syndrome.

Besides a focused personal and family history, physical examination clues may be an

indispensable tool in the early diagnosis.

References

1. Sanna-Cherchi, S, Ravani, P, Corbani, V, et al. Renal outcome in patients with congenital anomalies of the kidney and urinary tract. *Kidney Int.* 2009; 76 (5): 528-33.
2. Neild GH. Primary renal disease in young adults with renal failure. *Nephrol Dial Transplant.* 2010; 25 (4): 1025-32.
3. Zaffanello M, Brugnara M, Zuffante M, Franchini M, Fanos V. Are children with congenital solitary kidney at risk for lifelong complications? A lack of prediction demands caution. *Int Urol Nephrol.* 2009; 41 (1): 127-35.
4. Russell-Eggitt I, Bockenhauer D. The blind kidney: disorders affecting kidneys and eyes. *Pediatr Nephrol.* 2013; 28 (12): 2255-65.
5. Wang RY, Earl DL, Ruder RO, Graham JM Jr. Syndromic ear anomalies and renal ultrasounds. *Pediatrics.* 2001; 108 (2): E32.
6. Natarajan G, Jeyachandran D, Subramaniyan B, Thanigachalam D, Rajagopalan A. Congenital anomalies of kidney and hand: a review. *Clin Kidney J.* 2013; 6 (2): 144-9.
7. Lewis MA. Demography of renal disease in childhood. *Semin Fetal Neonatal Med.* 2008; 13 (3): 118-24.
8. Zentner GE, Layman WS, Martin DM, Scacheri PC. Molecular and phenotypic aspects of CHD7 mutation in CHARGE syndrome. *Am J Med Genet A.* 2010; 152A (3): 674-86.
9. Adalat S, Bockenhauer D, Ledermann SE, Hennekam RC, Woolf AS. Renal malformations associated with mutations of developmental genes: messages from the clinic. *Pediatr Nephrol.* 2010; 25 (11): 2247-55.
10. Fischbach BV, Trout KL, Lewis J, Luis CA, Sika M. WAGR syndrome: a clinical review of 54 cases. *Pediatrics.* 2005; 116 (4): 984-8.
11. Morisada N, Nozu K, Iijima K. Branchio-oto-renal syndrome: comprehensive review based on nationwide surveillance in Japan. *Pediatr Int.* 2014; 56 (3): 309-14.
12. Temtamy SA, Ismail S, Nemat A (April 2003). "Mild facial dysmorphism and quasidominant inheritance in Cenani-Lenz syndrome". *Clin. Dysmorphol.* 2003; 12 (2): 77-83.
13. Chakravarti HN, Ray S, Chakrabarti SK et al. Bardet-Biedl syndrome in two siblings: a rare entity revisited. *QJM.* 2015. pii: hcv114. [Epub ahead of print]
14. Evans JA, Vitez M, Czeizel A. Patterns of acrorenal malformation associations. *Am J Med Genet.* 1992; 1; 44 (4): 413-9.
15. Toka O, Maass PG, Aydin A et al. Childhood hypertension in autosomal-dominant hypertension with brachydactyly. *Hypertension.* 2010; 56 (5): 988-4.
16. Pereda A, Garin I, Garcia-Barcina M, et al. Brachydactyly E: isolated or as a feature of a syndrome. *Hypertension.* 2010; 56 (5): 988-94.
17. Woolf A, Stuart H, McKenzie E, Hilton E, Newman W. Urofacial syndrome: a genetic and congenital disease of aberrant urinary bladder innervation. *Pediatr Nephrol.* 2014; 29 (4): 513-8.
18. Seidel NE, Arlen AM, Smith EA, J. Clinical manifestations and management of prune-belly syndrome in a large contemporary pediatric population. *Urology.* 2015; 85 (1): 211-5.
19. Al-Gazali LI, Hamid Z, Hertecant J, Bakir M, Nath D, Kakadekar A. An autosomal recessive syndrome of choanal atresia, hypothelia/athelia and thyroid gland anomalies overlapping bamforth syndrome, ANOTHER syndrome and methimazole embryopathy. *Clin Dysmorphol.* 2002; 11(2):79-85.
20. Alazami AM, Shaheen R, Alzahrani F et al. FREM1 mutations cause bifid nose, renal agenesis, and anorectal malformations syndrome. *Am J Hum Genet.* 2009; 85 (3): 414-8.
21. Soliman NA, Ali RI, Ghobrial EE, Habib EI, Ziada AM. Pattern of clinical presentation of congenital anomalies of the kidney and urinary tract among infants and children. *Nephrology (Carlton).* 2015; 20 (6): 413-8.
22. Bondagji NS. Antenatal diagnosis, prevalence and outcome of congenital anomalies of the kidney and urinary tract in Saudi Arabia. *Urol Ann.* 2014; 6 (1): 36-40.
23. Hwang DY, Dworschak GC, Kohl S, et al. Mutations in 12 known dominant disease-causing genes clarify many congenital anomalies of the kidney and urinary tract. *Kidney Int.* 2014; 85 (6): 1429.
24. Song R, Yosypiv IV. Genetics of congenital anomalies of the kidney and urinary tract. *Pediatr Nephrol.* 2011; 26 (3): 353-64. Section of Pediatric Nephrology, Department of Pediatrics, Hypertension and Renal Center of

- Excellence, Tulane University Health Sciences Center, New Orleans, LA 70112, USA.
25. Weber S, Moriniere V, Knüppel T et al. Prevalence of mutations in renal developmental genes in children with renal hypodysplasia: results of the ESCAPE study. *J Am Soc Nephrol*. 2006; 17 (10): 2864-70.
 26. Weber S. Novel genetic aspects of congenital anomalies of kidney and urinary tract. *Curr Opin Pediatr*. 2012; 24 (2): 212-8.
 27. Woolf A, Stuart H, Newman W. Genetics of human congenital urinary bladder disease. *Pediatr Nephrol*. 2014; 29 (3): 353-60.
 28. Carmi R, Elbedour K, Wietzman D, Sheffield V, Shoham-Vardi I. Lowering the burden of hereditary diseases in a traditional, inbred community: ethical aspects of genetic research and its application. *Sci Context*. 1998; 11 (3-4): 391-95.
 29. Bulum B, Ozçakar ZB, Ustüner E et al. High frequency of kidney and urinary tract anomalies in asymptomatic first-degree relatives of patients with CAKUT. *Pediatr Nephrol*. 2013; 28 (11): 2143-7.
 30. McPherson E. Renal anomalies in families of individuals with congenital solitary kidney. *Genet Med*. 2007; 9 (5): 298-302.
 31. Kohl S, Hwang DY, Dworschak GC et al. Mild recessive mutations in six Fraser syndrome-related genes cause isolated congenital anomalies of the kidney and urinary tract. *Hum Genet*. 2015. [Epub ahead of print]
 32. Hindryckx A, De Catte L. Prenatal diagnosis of congenital renal and urinary tract malformations. *Facts Views Vis Obgyn*. 2011; 3 (3): 165-74.
 33. Westland R, Schreuder MF, Ket JC, van Wijk JA. Unilateral renal agenesis: a systematic review on associated anomalies and renal injury. *Nephrol Dial Transplant*. 2013; 28 (7): 1844-55.
 34. Ganesan I, Rajah S. Urological anomalies and chronic kidney disease in children with anorectal malformations. *Pediatr Nephrol*. 2012; 27 (7): 1125-30.
 35. Westland R, Kurvers RA, van Wijk JA, Schreuder MF. Risk factors for renal injury in children with a solitary functioning kidney. *Pediatrics*. 2013; 131 (2): e478-85.
 36. Westland R, Schreuder MF, van Goudoever JB, Sanna-Cherchi Svan Wijk JA. Clinical implications of the solitary functioning kidney. *Clin J Am Soc Nephrol*. 2014; 9 (5): 978-86.

تسخير الفحص السريري لتشخيص عيوب الكلى والمسالك البولية الخلقية

كمال عقل¹

1- قسم طب الأطفال، مستشفى الجامعة الأردنية، كلية الطب، الجامعة الأردنية، عمان، الأردن

الملخص

الهدف: مراجعه الأدبيات لمعرفة مدى استخدام الفحص السريري لتشخيص عيوب الكلى والمسالك البولية الخلقية.
الطريقة: مراجعه موقع ب ب مد على مدى 40 عاماً لمعرفة ما نشر عن تسخير الفحص السريري لتشخيص عيوب الكلى والمسالك البولية الخلقية.

النتائج: كان هناك فله من الأوراق التي تركز على أهمية الفحص السريري لتشخيص العيوب الخلقية للكلى والمسالك البولية عند الأطفال.

الكلمات الدالة: خلقي، الكلية، فحص.