Congenital Anomalies of the Kidney and Urinary Tract in Patients with Hirschsprung Disease

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ABSTRACT

Objective: To determine the frequency and types of congenital anomalies of the kidney and urinary tract (CAKUT) in patients with Hirschsprung disease.

Study Design: An observational cross-sectional study.

Place and Duration of the Study: Department of Paediatric Surgery, National Institute of Child Health, Karachi, Pakistan, from June to December 2022.

Methodology: All patients with biopsy-proven Hirschsprung disease were included. Ultrasound was done to find out the anatomical and structural anomalies of the kidney and urinary tract. Functional assessment was done by renal function tests and MAG3 radioisotope scan where indicated. Fisher's exact test was applied to find out the association. A $p \leq 0.05$ was taken as significant.

Results: Out of a total of 83, 15 (18.0%) patients had CAKUT. The mean age of the study population was 5.5 ± 2.3 years. It included 61 (73.5%) males and 22 (26.5%) females. No significant association was found between the type of Hirschsprung disease and CAKUT ($p = 0.7$). The gender distribution between CAKUT patients was also insignificant ($p = 0.7$). Renal hypoplasia was the most common anomaly found in six patients followed by hydronephrosis due to pelvi-ureteric junction obstruction in four children. All of these children were asymptomatic. Five male patients had undescended testis.

Conclusion: Nearly a fifth of the children with Hirschsprung disease had CAKUT of whom renal dysplasia was the most common anomaly. There was no gender predilection and patients were asymptomatic regarding the urinary system. A routine ultrasound abdomen is a good screening investigation for identifying CAKUT.

Key Words: *Hirschsprung disease, Kidney and urinary tract, Congenital diseases of the urinary tract, Congenital anomalies.*

How to cite this article: Mehmood M, Akhtar J, Zamir N. Congenital Anomalies of the Kidney and Urinary Tract in Patients with Hirschsprung Disease. *J Coll Physicians Surg Pak* 2024; **34(11)**:1334-1337.

INTRODUCTION

Congenital anomalies of the kidney and urinary tract (CAKUT, a recently coined acronym), is a heterogeneous group of anomalies that include a number of conditions that result from the aberration in the embryological development of the whole of the urinary tract. It includes anomalies related to the position, rotation, and blood supply as well as parenchymal malformations of the kidneys (agenesis, hypoplasia, or dysplasia) and of lower urinary tract including the urinary bladder and urethra.[1] The aetiology of this condition is not known. However, genetic and molecular changes at the time of renal and urinary tract development *in-utero* are implicated. The importance of recognising this condition at an early stage is important as these developmental anomalies can lead to end-stage kidney disease which may result in kidney replacement therapy in children at later age.[2,3]

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Received: July 10, 2024; Revised: August 29, 2024; Accepted: October 04, 2024
DOI: https://doi.org/10.29271/jcpsp.2024.11.1334

The overall prevalence of CAKUT in population-based studies varies between 4 to over 100 cases per 10,000 individuals. In addition, extrarenal anomalies and diseases are also reported more frequently in patients with CAKUT. This includes anomalies of the cardiac, genito-reproductive, ocular, and central nervous systems.[4] Hirschsprung disease which is characterised by the absence of the enteric ganglion cells is reported to result from the mutations of RET proto-oncogene. It is considered a major candidate gene causing Hirschsprung disease. This is the major aetiological factor in the development of long segment, total colonic, and total intestinal aganglionosis verities of Hirschsprung disease. CAKUT documented in patients with Hirschsprung disease is due to the common genetic pathway for the development of the enteric nervous system and kidneys. This is considered as a novel genetic mutation.[5,6] This specific genetic relationship is being explored further.

The frequency of CAKUT in patients with Hirschsprung disease is variable. After coining of the acronym CAKUT, studies that specifically investigated the association of Hirschsprung's disease and CAKUT reported a prevalence of 14.3%. This highlighted about five-fold increase when compared with previously reported figures.[7,8]

Most of the anomalies of the kidney and urinary tract remain asymptomatic in early life. However, Hirschsprung's disease,

especially the syndromic type, affects the quality of life of the patients. Presence of CAKUT adds morbidity for these children. It is important to investigate the associated conditions of the kidney and urinary tract so that treatment, if required, may be started early to prevent further deterioration of the renal reserves. This study was conducted to find out the frequency of CAKUT in patients with Hirschsprung disease including the functional status of the kidneys. This is expected to add evidence-based data on this subject.

METHODOLOGY

This was an observational cross-sectional study conducted at the Department of Paediatric Surgery, National Institute of Child Health, Karachi, Pakistan, from June to December 2022. The sample size was calculated using OpenEpi version 3, taking the estimated prevalence of CAKUT associated with Hirschsprung disease as 10.3%,[8] a 7% margin of error, and confidence level as 95%, which came out to be 83.

All diagnosed patients of Hirschsprung disease who were managed in the institution were enrolled. Children presenting with constipation due to any other reason and those with renal and other urinary tract conditions not associated with Hirschsprung disease were excluded. The study was approved by the Institutional Review Board of National Institute of Child Health (Approval Number: IERB-04/2022). Parents of the patients were informed about the details of the study and consent was taken.

Patients of Hirschsprung disease were examined and any symptoms related to the urinary tract were inquired. Abdominal examination was carried out for abdominal mass. Examination of external genitalia was done including penis, scrotum, and vestibule. All patients had ultrasound done to document the structural anomalies of the urinary tract and echogenicity of renal parenchyma was recorded. Renal function tests were advised in all patients. CT pyelogram and radioisotope MAG-3 scan were advised where indicated.

A form was designed in which demographic details were entered. Clinical examination findings as well as biochemical and radiological results were recorded. These were then entered into IBM Statistical Package for the Social Sciences (SPSS) version 23 for analysis. Data were analysed using SPSS 23 software. Frequencies and percentages were computed for categorical variables such as gender and type of anomalies. Mean with standard deviations were calculated for numeric variables such as age. Descriptive statistics were used for the presentation of demographic data. Fisher's exact test was used to find the association between the gender and types of Hirschsprung disease with CAKUT. A $p \leq 0.05$ was considered as statistically significant.

RESULTS

A total of 83 children with a mean age of 5.5 ± 2.3 years were included. The cohort included 61 (73.5%) males and 22 (26.5%) females. The majority of the patients (n = 71, 85.5%) had a classical short segment Hirschsprung's disease (14 having CAKUT). Twelve (14.5%) patients had long segment disease (one having CAKUT). There was no patient with total colonic aganglionosis and syndromic features. CAKUT was found in 15 patients accounting for 18.1%. Five male patients had associated genital anomalies as well. The type of Hirschsprung disease and gender distribution showed no statistically significant association with CAKUT ($p = 0.7$).

Right kidney was affected in five patients while left in three patients. Of these, four patients had bilateral renal involvement. The abnormal small kidneys were defined as a size less than two standard deviations below the expected mean for the corresponding age. This was the most common abnormality found in six patients (Table I). Three patients showed bilateral small-size kidneys. All these patients were asymptomatic with normal renal function tests. The second most common finding was hydronephrosis of kidneys, based upon antero-posterior diameter of renal pelvis (APD), noted in four patients and all of them were male. These patients were followed with renal function tests, urine analysis, and MAG3 radioisotope scan. The results of the scan are given in Table II.

One patient presented at the age of one month with biopsy-proven Hirschsprung's disease. This neonate had symptoms of dribbling of urine. Workup showed bilateral hydronephrosis with hydroureter. Voiding cystourethrography (VCUG) showed a posterior urethral valve with bilateral grade IV vesicoureteral reflux. Cryptorchidism was found in five patients while two had hypospadias. Five patients presented with symptoms of dysuria and documented urinary tract infection. Ultrasound performed in these patients showed urinary tract calculi, three children with urinary bladder, and two renal calculi on the right side.

Table I: Types of congenital anomalies of the kidney, urinary, and genital tracts.

Anomalies	Male	Female	Total	p-value
Renal Anomalies				
Hypoplasia of the kidney	3	3	6	
Hydronephrosis secondary to PUJO	4	0	4	
Ectopic kidney in left lower lumbar region	0	1	1	
Simple cortical cyst of the right kidney	1	0	1	
Urethral anomalies				**0.7**
Hypospadias	2	0	2	
Posterior urethral valves	1	0	1	
Genital anomalies				
Cryptorchidism	5	0	5	

Table II: Functional status of patients with hydronephrosis.

Patient number	Ultrasound findings	MAG3 findings
1	Bilateral minimal hydronephrosis with APD 0.3cm	Right kidney: 55% Left kidney: 45%
2	Right kidney: Moderate hydronephrosis with APD 1.2cm	Right kidney: 46% Left kidney: 54%
3	Left kidney: Mild hydronephrosis with APD 0.4cm	Right kidney: 50% Left kidney: 50%
4	Left kidney: Moderate hydronephrosis with APD 1.1cm	Right kidney: 56% Left kidney: 44%

DISCUSSION

The prevalence of CAKUT in patients with Hirschsprung disease in this study was 18.1%. However, the exact prevalence of CAKUT in patients with Hirschsprung disease is still under investigation. Different percentages are reported in literature though there is a consensus that the prevalence of CAKUT is higher in patients with HD than in the general population. Prato *et al.* reported a prevalence of 25% in a cohort of 84 patients with Hirschsprung disease in their study.[7] They reported a 4- to 6-fold higher than expected incidence of CAKUT in Hirschsprung disease which corresponds to a 3- to 18-fold higher risk.

A number of genes have been found associated with Hirschsprung disease.[7] Rearranged during transfection (RET) is considered as the most important gene causing Hirschsprung disease as it influences the developing enteric nervous system. RET signalling pathway is equally important for the development of the kidney and urinary systems.[9-11] Thus, CAKUT is expected to be associated with Hirschsprung disease. Almost all cases of CAKUT were found in patients with short segment Hirschsprung disease. This reflects that the patients with non-syndromic variety can also have CAKUT.

The importance of CAKUT lies in the fact that many of the affected individuals remain asymptomatic. The impairment of renal function manifests later in life. The renal hypoplasia and dysplasia that represent critical reduction in renal mass, lead to gradual loss of functional parenchyma and functional impairment over the years, as critical renal mass represented by fewer nephrons, cannot sustain for long.[12] This will lead to the gradual onset of renal failure. In this study, one-third of the patients had renal hypoplasia. The renal function assessment showed a slight decrease in the differential function on radioisotope scan in patients with pelvic-ureteric junction obstruction. It is hypothesised that the paucity of renal mass may be compensated early by other kidney or by the remaining nephrons. However, over a period of time this may progress to glomerular sclerosis. These patients were picked up incidentally on screening ultrasound in this study. It is therefore important to subject all patients with Hirschsprung disease for ultrasound to identify patients with CAKUT early.

Rasouly and Lu coined a phrase "congenital anomalies of the lower urinary tract" with an acronym of CALUT. This includes a number of anomalies of the ureter, urinary bladder, and urethra. Thus, there is an overlap between the anomalies included in CAKUT and CALUT. They also reported an overview of the developmental processes of the lower urinary tract with different genes involvement and signalling pathways controlling the developmental processes. In the era of genetic and genomic testing, such a knowledge may help predicting the future of the affected individuals.[13] In this study, three patients had anomalies of the urethra.[5] One patient had posterior urethral valves.

Embryological development of the genital system parallels with the urinary system. Gonads develop from urogenital ridge, and the outflow tract of the testis is contributed by the remnant of mesonephric ducts. The venous drainage of the left testis flows into the left renal vein. Therefore, it is hypothesised that genital anomalies may be a part of the spectrum of associated anomalies, as many of the embryological aberrations may have similar origins.[14,15] In this study, five patients with Hirschsprung disease had undescended testis. Such presentation has been reported in literature as well.[16,17]

Hirschsprung disease and CAKUT, both have aberrations in common genetic signalling pathway. Prenatal imaging is helpful in the detection of common anomalies of the kidneys and urinary tract. It is reported that CAKUT constitute 20 - 30% of all major birth defects.[18] Parallel with the antenatal diagnostic technologies, the advancement in the genetic sequencing revealed additional information about different associations such as CAKUT and Hirschsprung disease. This may help in developing diagnostic tests for the identification of these anomalies in the future.[19] This will improve understanding about the pattern of the diseases as well as planning early treatment so as to improve the quality of life of the affected individuals.[20] There are a few limitations of this study. It is a single-centred study with a cross-sectional design. A cohort study with larger sample size spanning over decades can provide more evidence with regards to CAKUT's impact on quality of life.

CONCLUSION

Number of patients with Hirschsprung disease were found to have CAKUT and genital anomalies. Renal hypoplasia was found in one-third of the patients and all were asymptomatic with a potential to develop renal impairment later in life. Ultrasound must be incorporated into the diagnostic workup of patients with Hirschsprung disease to document anomalies early in infancy.

ETHICAL APPROVAL:
This study was approved by the Institutional Review Board of

the National Institute of Child Health, Karachi, Pakistan (Approval Number: IERB-04/2022).

PATIENTS' CONSENT:
Parents of the children were informed about the details of the study and their consents were taken to participate. They were informed that the cumulative results of the study (with personal details kept confidential) would be published and their permission was taken.

COMPETING INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
MM: Conception and design, acquisition, analysis and interpretation of data, and manuscript writing and revision.
JA: Analysis and interpretation of data, manuscript writing, and revision.
NZ: Critical evaluation of the manuscript and revision.
All authors approved the final version of the manuscript to be published.

REFERENCES

1. Stonebrook E, Hoff M, Spencer JD. Congenital anomalies of the kidney and urinary tract: A clinical review. *Curr Treat Options Pediatr* 2019; **5(3)**:223-35. doi: 10.1007/s40746-019-00166-3.
2. Murugapoopathy V, Gupta IR. A Primer on congenital anomalies of the kidneys and urinary tracts (CAKUT). *Clin J Am Soc Nephrol* 2020; **15(5)**:723-31. doi: 10.2215/CJN.12581019.
3. Costigan CS, Rosenblum ND. Anatomy and embryology of congenital surgical anomalies: Congenital anomalies of the kidney and urinary tract. *Semin Pediatr Surg* 2022; **31(6)**: 151232. doi: 10.1016/j.sempedsurg.2022.151232.
4. Hays T, Thompson MV, Bateman DA, Sahni R, Tolia VN, Clark RH, *et al.* The prevalence and clinical significance of congenital anomalies of the kidney and urinary tract in preterm infants. *JAMA Netw Open* 2022; **5(9)**:e2231626. doi: 10.1001/-jamanetworkopen.2022.31626.
5. Liu JL, Wang XW, Liu CH, Gao DMX, Jiang XY, Mao JH, *et al.* Children genetic kidney disease database (CCGKDD), "internet plus" nephrology alliance of the national center for children's care department of nephrology, children's hospital of fudan university, national children's medical center, Shanghai, China. Genetic spectrum of CAKUT and risk factors for kidney failure: A pediatric multicenter cohort study. *Nephrol Dial Transplant* 2022; **38(9)**:1981-91. doi: 10.1093/ndt/gfac338.
6. Tomuschat C, Puri P. RET gene is a major risk factor for Hirschsprung's disease: A meta-analysis. *Pediatr Surg Int* 2015; **31(8)**:701-10. doi: 10.1007/s00383-015-3731-y.
7. Prato AP, Musso M, Ceccherini I, Mattioli G, Giunta C, Ghiggeri GM, *et al.* Hirschsprung disease and congenital anomalies of the kidney and urinary tract (CAKUT): A novel syndromic association. *Medicine (Baltimore)* 2009; **88(2)**:83-90. doi: 10.1097/MD.0b013e31819cf5da.
8. Graneli C, Marschall Sima H, Borjesson A, Hagelsteen K, Arnbjornsson E, Stenstrom P. Urinary tract anomalies and urinary tract dysfunction in children with Hirschsprung disease-Is follow-up indicated? *J Pediatr Surg* 2019; **54(10)**: 2012-6. doi: 10.1016/j.jpedsurg.2018.12.006.
9. Eelen J, Miserez M, Mekahli D, Hoffman I. Hirschsprung disease and congenital anomalies of the kidney and urinary tract (CAKUT): A genetic disorder or just a coincidence? *Belgian J Paediatr* 2020; **22(3)**:126-9.
10. Karim A, Tang CS, Tam PK. The emerging genetic landscape of hirschsprung disease and its potential clinical applications. *Front Pediatr* 2021; **9**:638093. doi: 10.3389/fped.2021.638093.
11. Cardinal T, Bergeron KF, Soret R, Souchkova O, Faure C, Guillon A, *et al.* Male-biased aganglionic megacolon in the TashT mouse model of Hirschsprung disease involves upregulation of p53 protein activity and Ddx3y gene expression. *PLoS Genet* 2020; **16(9)**:e1009008. doi: 10.1371/journal.p-gen.1009008.
12. Pope JC, Brock JW, Adams MC, Stephens FD, Ichikawa I. How they begin and how they end: Classic and new theories for the development and deterioration of congenital anomalies of the kidney and urinary tract, CAKUT. *J Am Soc Nephrol* 1999; **10(9)**:2018-28. doi: 10.1681/ASN.V1092018.
13. Rasouly HM, Lu W. Lower urinary tract development and disease. *Wiley Interdiscip Rev Syst Biol Med* 2013; **5(3)**: 307-42. doi: 10.1002/wsbm.1212.
14. Rodriguez MM. Congenital Anomalies of the kidney and the urinary tract (CAKUT). *Fetal Pediatr Pathol* 2014; **33(5-6)**: 293-320. doi: 10.3109/15513815.2014.959678.
15. Shrateh ON, Jobran AWM, Jaber S, Kahla A, Shker, Arafeh WA. A rare association between crossed fused renal ectopia, urethral stricture, bilateral cryptorchidism, and sub-coronal hypospadias in a non-syndromic 6-year-old child. *J Pediatr Surg Case Rep* 2023; **89**:102561. doi: 10.1016/j.epsc.2022.102561.
16. Pini Prato A, Rossi V, Mosconi M, Holm C, Lantieri F, Griseri P, *et al.* A prospective observational study of associated anomalies in Hirschsprung's disease. *Orphanet J Rare Dis* 2013; **8**:184. doi: 10.1186/1750-1172-8-184.
17. Amiel J, Sproat-Emison E, Garcia-Barcelo M, Lantieri F, Burzynski G, Borrego S, *et al.* Hirschsprung disease, associated syndromes and genetics: A review. *J Med Genet* 2008; **45(1)**:1-14. doi: 10.1136/jmg.2007.053959.
18. Stein D, McNamara E. Congenital anomalies of the kidneys and urinary tract. *Clin Perinatol* 2022; **49(3)**:791-8. doi: 10.1016/j.clp.2022.06.002.
19. Lee KH, Gee HY, Shin JI. Genetics of vesicoureteral reflux and congenital anomalies of the kidney and urinary tract. *Investig Clin Urol* 2017; **58**:S4-13. doi: 10.4111/icu.2017.58.S1.S4.
20. Kagan M, Pleniceanu O, Vivante A. The genetic basis of congenital anomalies of the kidney and urinary tract. *Pediatr Nephrol* 2022; **37(10)**:2231-43. doi: 10.1007/s00467-021-05420-1.