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Congenital Hypothyroidism and Kidney and Upper Urinary Tract Anomalies in Neonates; Is There Any Association?

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Abstract

Background: In the last twenty years, there has been a noticeable rise in the occurrence of extra-thyroidal congenital anomalies in people diagnosed with Congenital Hypothyroidism (CH). This study seeks to investigate the frequency of additional Kidney/Urinary Tract Anomalies (KUTAs) in a group of children with confirmed Permanent Congenital Hypothyroidism (PCH).

Methods: This retrospective study was conducted in Isfahan, Iran, utilizing data from the newborn screening database, where TSH test results from the Guthrie heel pinprick test were accessible. Patients diagnosed with PCH were included in the study. We excluded patients who died before three years and those who migrated to other provinces. All participants underwent ultrasonography and additional diagnostic measures, if necessary, to assess the presence of KUTAs.

Results: The study included 1091 patients with CH, of whom 74 (6.78%) also had additional KUTAs. Specific anomalies included hypospadias (1.5%), undescended testes (UDT) (1.2%), renal agenesis (0.6%), pyelocaliceal system anomalies (1.6%), hydrocele/varicocele (0.7%), and vesicoureteral reflux (0.1%). Regression analysis showed a higher likelihood of KUTAs in cases of Cesarean Section (C/S) delivery and a history of first-degree consanguineous marriage (OR=2.27, 95% CI (0.4-13.04); OR=3.34, 95% CI (0.43, 26.07), respectively). However, these observed associations were not statistically significant (P-value>0.05).

Conclusion: Our findings highlight a significant link between PCH and the occurrence of KUTAs. Therefore, a thorough kidney assessment is necessary for all confirmed PCH patients.

Key Words: Congenital Hypothyroidism, Congenital Abnormalities, Kidney, Urinary Tract.

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1- INTRODUCTION

Thyroid hormones play a crucial role in regulating growth, metabolism, and physiological functions across various organ systems. Congenital hypothyroidism (CH) is a prevalent endocrinopathy and a primary preventable cause of neonatal mental developmental disabilities. Additionally, CH is associated with an elevated incidence of other congenital anomalies. It manifests as variable dysfunction of the Hypothalamic–Pituitary–Thyroid (HPT) axis, presenting at birth and resulting in inadequate Thyroid Hormone (TH) production, leading to varying degrees of thyroid deficiency (1-3).

In recent years, the global incidence of CH has witnessed a rise, attributed to factors such as broader diagnostic criteria, shifting demographics, and increased survival rates of preterm infants (4, 5). Many regions worldwide implement newborn screening programs for CH (6), with incidence rates varying internationally, such as 1:2320 in Italy (7), 1:469 in Turkey (8), 1:800 in Greek Cypriot populations (9), and 1:2372 in the United States (10). Iran reports an incidence of approximately 2:1000 births (11), varying across districts, ranging from 1.6 to 4.4 per 1,000 live births (12). In Isfahan province, central Iran, the prevalence rate was 2.36 per 1,000 live births in 2015 (13, 14).

While thyroid dysgenesis accounts for 85% of CH cases, dyshormonogenesis is prevalent in our country, as per research findings. Genetic factors have been explored as contributors to CH, with familial cases occurring at a rate 15 times greater than expected (15). Despite this, over 90% of monozygotic twin pairs exhibit discordance for thyroid dysgenesis, suggesting a significant role for post-zygotic events in thyroid gland developmental abnormalities (16). Recent studies highlight the importance of transcription factors like paired box gene 8 (PAX-8) in the embryonic thyroid gland's development and migration, underscoring its regulatory role (17).

Kidney/Urinary Tract Anomalies (KUTAs) are prevalent, constituting around 30% of birth anomalies (18) and being major contributors to End-Stage Renal Disease (ESRD) in children. Research has linked mutations in the PAX-8 gene to CH patients with KUTAs, as this gene plays a crucial role in the kidney's mesonephric duct origin, ureteric bud, and primary collecting ducts (19). The multifaceted impacts of thyroid hormones are orchestrated by the thyroid Hormone Receptors (TRs), a cluster of transcription factors pivotal for the maturation of the mammalian nervous system (20). These TRs, which possess a strong binding affinity for T3, belong to the steroid/thyroid hormone receptor superfamily. Following T3 attachment, they engage with Hormone Response Elements (HREs) situated in the promoter regions of target genes (21). The THRA gene encodes two primary splice variants—TRα1 and TRα2—while the THRB gene encodes two variations—TRβ1 and TRβ2. TRα1 finds its main expression in the heart, bone, and skeletal muscle, whereas TRα2 exhibits a widespread distribution in the body. Predominantly found in the brain, liver, and kidney, TRβ1 is complemented by TRβ2, which is prevalent in the pituitary, retina, and cochlea. Notably, TRα1, TRβ1, and TRβ2 exhibit comparable affinities for T3 (22).

Considering the significance of congenital anomalies associated with CH and the limited studies on KUTAs in these patients, assessing these anomalies in newborns with CH appears warranted (17, 23). Considering the widespread global screening for CH and the relatively lower rate of kidney and urogenital tract anomalies screening, CH diagnosis could signal the need for additional examinations

for KUTAs. This study aims to determine the prevalence of KUTAs in primary permanent CH patients.

2- MATERIALS AND METHODS

2-1. Design and participants

This retrospective analysis included patients diagnosed with permanent CH. The study cohort was identified through the Isfahan province's newborn screening (NBS) program spanning from March 2007 to March 2016. Those who relocated without NBS oversight in Isfahan province, or who passed away before the age of three were excluded.

2-2. Data Collection

Briefly, the primary TSH-based screening with T4 backup measurement was employed to detect CH. The whole-blood heel prick samples were collected 3–7 days after birth. Neonates with a Guthrie TSH test 5 mIU/L on the first TSH screening test were recalled to repeat the screening test; those with TSH 5–9.9 mIU/L were recalled for complementary tests, and those with TSH 10 mIU/L were recalled for confirmatory venous sampling. For confirmed patients, 10–15 μg/kg/day of levothyroxine was prescribed. Further follow-up was accomplished based on growth indices, T4, and TSH profile measurements. At the age of three, the TCH and PCH were determined by normal and abnormal TSH and T4 values (TSH <5 mIU/L and T4 >6.5 μg/dl) following the withdrawal of levothyroxine for a month, respectively.

Information on patients suffering from the PCH, including clinical comorbidities, perinatal complications, anomalies, and parental medical histories, was gathered from the NBS database. Ultrasound findings related to anomalies in various areas such as the shaft, testes, urethra, ureter, pyelocaliceal system, and renal agenesis were also recorded.

2-2-1. Examination of Kidney/Urinary Tract Anomalies (KUTAs):

The evaluation of kidney/urinary tract anomalies (KUTAs) involved a comprehensive assessment combining clinical examinations and diagnostic procedures. Initially, abdominal and pelvic ultrasounds were performed by skilled radiologists. If initial radiographic scans were unavailable, families were contacted, and additional ultrasounds were arranged.

Ultrasound (US) is typically the primary imaging modality for urinary tract anomalies, due to its non-invasiveness, accessibility, cost-effectiveness, and lack of ionizing radiation. However, its limitations include operator- and patient-dependence and restricted visualization of the entire collecting system. Contrast-enhanced US, particularly voiding urosonography, has gained traction, especially in pediatric patients, for evaluating vesicoureteral reflux and urethral abnormalities.

Voiding Cystourethrogram (VCUG) has traditionally been used to diagnose vesicoureteral reflux and urethral abnormalities. Recently, voiding urosonography has emerged as a reliable first-line alternative to VCUG in specialized centers for assessing these conditions. While both procedures involve bladder catheterization, voiding urosonography stands out as a radiation-free examination, allowing simultaneous evaluation of morphological features and reflux, whereas VCUG offers the advantage of visualizing the entire collecting system at once.

CT and MR urography were employed to evaluate the upper urinary tract, providing detailed visualization of the entire collecting system's anatomy. MRI offers additional insights into perfusion and excretion functions and is preferred for pediatric patients and individuals requiring repeated imaging due to its lack of

ionizing radiation and suitability for those allergic to iodinated contrast agents.

All imaging scans were performed at a single center in Isfahan by two skilled radiologists. Suspected cases underwent further diagnostic procedures, including VCUG, Dimercapto succinic acid (DMSA) scans, Tc99m-DTPA, and abdominal and pelvic CT scans as necessary for each patient.

2-3. Data Analysis

Continuous variables were expressed as mean±standard deviation, while discrete variables were presented as numbers and percentages. Normality and homogeneity of the data were assessed using the Shapiro-Wilk and Leven's tests, respectively. Depending on data homogeneity, comparisons of continuous variables were conducted using the independent T-test/analysis of variance (ANOVA) with post hoc tests or the Mann-Whitney-U test, while Chi-square tests were utilized for discrete variables. The association between CH and KUTAs was evaluated through Pearson correlation and logistic regression analysis, with logistic regression results reported as Odds Ratios (OR) with 95% Confidence Intervals (CI). Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS Inc., version 22.0, Chicago, IL, USA), with a significance level set at $P < 0.05$.

3- RESULTS

Throughout the study period, 1091 participants were enrolled, with a male gender predominance (53.7%). Of these, 74 patients (6.78%) exhibited kidney/urinary tract anomalies (KUTAs). Baseline, clinical, and medical history characteristics of Congenital Hypothyroidism (CH) patients with and without KUTAs are detailed in **Table 1**.

According to this table, most of the infants were born in summer, and the average age of the parents of the infants was 32.82 and 28.64, respectively. The average head circumference and birth height were equal to 34.63 and 48.07 cm, respectively. The average birth weight was 2.93 Kg.

CH patients with/without KUTAs displayed no significant differences in parental age during pregnancy, parental education level, history of consanguineous marriage, types of delivery, anthropometric indices at birth, and perinatal complications (P-value > 0.05) (Table 1).

Specific KUTAs, including hypospadias, undescended testes (UDT), renal agenesis, pyelocaliceal system anomalies, hydrocele/varicocele, vesicoureteral reflux, and posterior urethral valve, constituted 1.5%, 1.2%, 0.6%, 1.6%, 0.7%, 0.1%, and 0%, respectively (Table 2).

Table 3 outlines the association between different KUTAs and Permanent Congenital Hypothyroidism (PCH). Pearson correlation analysis revealed a significant positive association between CH and various KUTAs (P-value <0.0001), with the highest correlations observed for pyelocaliceal system anomalies and hypospadias compared to other anomalies (r=0.47 and 0.45, respectively).

Regression analysis indicated a more pronounced impact of Cesarean Section (C/S) delivery (compared to natural vaginal delivery) and a history of first-degree consanguineous marriage (compared to the absence of consanguineous marriage history) on the presence of KUTAs (OR=2.27, 95%CI (0.4-13.04); OR=3.34, 95%CI (0.43, 26.07), respectively). Additionally, the analysis revealed a lower impact of male gender compared to female gender on the presence of KUTAs (OR=0.27, 95%CI (0.04-1.86)). However, these observed outcomes were statistically insignificant (P-value>0.05) (Table 3).

Table-1: General characteristics of the study population according to infant's kidney anomalies at birth.

Variables		Total (n=1091)	infant's kidney anomalies at birth		P
			Yes (74)	No (1017)	
Male (%)		585 (53.7)	58 (78.4)	527 (51.9)	<0.0001
Season of birth	Spring	259 (24.4)	16 (22.5)	243 (24.5)	0.25
	Summer	298 (28)	16 (22.5)	282 (28.4)	
	Autumn	230 (21.6)	22 (31)	208 (21)	
	Winter	276 (26)	17 (23.9)	259 (26.1)	
Mother age (year)		28.64±5.26	27.55±5.24	28.71±5.26	0.25**
Father age (year)		32.82±5.72	32.39±6.67	32.85±5.66	0.68**
Birth weight(kg)		2.93±0.69	2.71±0.85	2.95±0.68	0.26
Birth height (cm)		48.07±6.87	46.20±9.72	48.18±6.66	0.33
Head circumference (cm)		34.63±2.99	34.60±4.47	34.64±2.89	0.69
Neonatal TSH from the heel prick test		45.76±93.06	56.03±110.16	45.07±91.83	0.06
Maternal thyroid dysfunction	Hypothyroidism	176 (16.1)	14 (18.9)	162 (15.9)	0.58
	Hyperthyroidism	9 (0.8)	0	9 (0.9)	
Paternal thyroid dysfunction	Hypothyroidism	51 (4.7)	3 (4.1)	48 (4.7)	0.74
	Hyperthyroidism	7 (0.6)	0	7 (0.7)	
Parental consanguinity	First degree	159 (14.6)	14 (18.9)	145 (14.3)	
	Second degree	91 (8.3)	6 (8.1)	85 (8.4)	0.55
Mother education	Non academic	273 (58.6)	21 (75)	252 (57.5)	0.07
	Academic	193 (41.4)	7 (25)	186 (42.5)	
Father education	No University Education	292 (63.1)	19 (70.4)	273 (62.6)	0.42

* Results from Mann-Whitney test and chi-square test.

** Result from independent samples t-test.

Table-2: Prevalence of kidney-urinary tract anomalies in CH patients.

Variables	Infant's kidney anomalies at birth
Hypospadias (%)	16 (1.5)
UDT (%)	13 (1.2)
Renal Agenesis (%)	7 (0.6)
Hydronephrosis/UPJO/Renal Stone (%)	17 (1.6)
Hydrocele/Varicocele (%)	8 (0.7)
Vesicoureteral Reflux (%)	1 (0.1)
Posterior Urethral Valve (%)	0
Not Determined Renal Anomaly (%)	19 (1.7)

UDT: Undescended testes; UPJO: Ureteropelvic joint obstruction

Table-3: Odds ratios (ORs) and 95% confidence intervals (95% CIs) for the association between the infant's kidney anomalies and other characteristics at birth.

Characteristics		OR (95% CI)	P-value
Sex	Male	0.27 (0.04-1.86)	0.18
	Female	Ref	
Mother's age (year)		1.08 (0.86-1.36)	0.49
Father's age (year)		0.85 (0.69-1.04)	0.11
Birth weight(kg)		1.80 (0.34-9.48)	0.49
Birth height (cm)		0.98 (0.78-1.24)	0.88
Screening TSH from the heel prick test		0.99 (0.99-1.001)	0.12
Consanguinity	First degree	3.34 (0.43-26.07)	0.25
	No familial relationship	0.89 (0.12-6.76)	0.91
	Second degree	Ref	
Type of delivery	C/S	2.27 (0.40-13.04)	0.36
	Natural	Ref	

C/S: Cesarean Section

4- DISCUSSION

The primary objective of this study was to assess the prevalence of Kidney and Urinary Tract Anomalies (KUTAs) as comorbidities in newborns with Permanent Congenital Hypothyroidism (PCH). Our findings indicated a KUTA prevalence of 6.78%.

Comparisons with existing literature reveal varying prevalence rates. Kumar et al.'s analysis of New York State newborn screening data from 1992 to 2005 reported a significantly increased prevalence of KUTAs in Congenital Hypothyroidism (CH) with an Odds Ratio (OR) of 4.8 (3.7-6.3) (24). In contrast, Cassio et al. found a lower prevalence of internal urogenital system malformations (0.43%) in their study of 235 subjects with CH (25).

Reddy et al., in India, reported no cases of urogenital anomalies among 70 children with CH (26). Yousefichaijan et al., in a case-control study on 200 children aged 3 months to 1 year, showed that the frequency of renal and upper urinary tract anomalies among children with CH was significantly higher than that in the control group (OR = 3; CI 95%: 1.6-5.4; P = 0.001)(23). Elkholy et al., in a study on 44 children with CH, reported that the prevalence of urological anomalies was 6.81% (27).

Discrepancies in prevalence rates across studies underscore the complex interplay of genetic and environmental factors influencing CH and KUTAs. Our study revealed a higher prevalence of hypospadias and undescended testes (UDT) compared to other KUTAs, aligning with findings from Kumar et al., where hydronephrosis (0.037%) and hypospadias (0.027%) were the most prevalent KUTAs (24). Similarly, Yousefichaijan et al.'s study in Iran identified hypospadias and UDT as predominant KUTAs in children with CH (23).

In the investigation conducted by Wędrychowicz et al., it was observed that out of 54 newborns diagnosed with CH, twenty (37%) exhibited congenital anomalies in other organ systems. Specifically, cardiac defects were identified in 10 individuals (18.5%), abnormal respiratory symptoms in 5 cases (9.25%), abnormalities of the gastrointestinal system in 7 cases (12.96%), genitourinary abnormalities in

five cases (9.25%), nervous system abnormalities in 3 cases (5.55%), and musculoskeletal abnormalities in 6 cases (11.1%). Within the study group, five male children (9.25%) displayed genitourinary system defects. Among them, one child presented with cryptorchidism accompanied by hypospadias, and another with cryptorchidism alongside an inguinal hernia. Additionally, hydrocele was diagnosed in 2 children (40%), while one child (20%) was found to have hydronephrosis concurrent with a urinary tract infection. Furthermore, gastrointestinal anomalies were detected in three children (60%), including tracheoesophageal fistula and bile reflux. These findings underscore the importance of comprehensive evaluation and management of multi-system congenital anomalies in individuals with CH (28).

In a comprehensive systematic review conducted by Rose et al., it was highlighted that infants diagnosed with CH exhibit a heightened susceptibility to congenital anomalies, with a prevalence of 10% compared to 3% in the general population. Among these anomalies, cardiovascular irregularities such as pulmonary stenosis, atrial septal defect, and ventricular septal defect were frequently observed. Additionally, the review underscored the presence of dysmorphic features, neural tube defects, hip dysplasia, as well as renal and other urinary tract anomalies in this population. These findings emphasize the necessity for vigilant screening and management of various congenital anomalies in infants with CH (29).

However, in a study on CH patients in Egypt, the most frequent form of KUTAs was absent left kidney (19). Regional variations in prevalent KUTAs emphasize the importance of considering geographical and genetic factors. Although our study showed an insignificant relationship between maternal age, birth weight, and the prevalence of KUTAs, prior research by Abbasi et al. in East Azerbaijan, Iran, demonstrated a higher impact of shorter birth height and low birth weight on KUTAs in CH patients (30). These findings hint at the intricate interplay between demographic factors and congenital anomalies, necessitating further explorations.

Given the high incidence of CH in Iranian newborns, particularly attributed to intra-familial marriages, the study suggests a potential link between CH and KUTAs influenced by shared genetic factors (21).

About 15% of total PCH cases in Iran could be attributed solely to intra-family marriages (4). As stated before, KUTA and CH are influenced by similar genetic factors (14). We can conclude that with higher intra-familial marriages, children born with CH and KUTA could become a more common sight. Further investigations into the developmental associations between CH and KUTAs are warranted to enhance our understanding of these comorbidities.

It is suggested that in future studies, due to the high prevalence of CH in Iran following consanguineous marriages, the parents of the patients are examined genetically and the cause of such disorders is determined. It is also recommended to examine patients in terms of different ethnicities.

4-1. Limitations of the study

Limitations of our study include the absence of exploration into extra-urinary tract malformations, the failure to evaluate KUTA frequency in first-degree relatives of CH patients, and the retrospective design. Despite these limitations, our study underscores the significance of a comprehensive examination for congenital anomalies in the kidneys and urinary tracts among patients with PCH. The authors of this study accept the possibility of uncertainty in the obtained results.

5- CONCLUSION

This study highlights a significant association between Permanent Congenital Hypothyroidism (PCH) and the prevalence of congenital anomalies in the kidneys and urinary tracts. The findings emphasize the importance of thorough examinations for such anomalies in all patients referred after a positive congenital hypothyroidism screen.

6- ETHICAL CONSIDERATIONS

Ethical approval was obtained from the local clinical research ethics committee (Ethical code: IR.MUI.MED.REC.1399.095).

7- ACKNOWLEDGEMENTS:

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