Original Article

# Hereditary renal tubular disorders: Single Iraqi center experience of 80 pediatric cases

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*Summary:*

**Background:** Hereditary renal tubular disorders (HRTDs) encompass various clinical syndromes and most of them have profound effects on child's growth and development,.

**Objectives:** was to review our experience at children welfare teaching hospital in Baghdad with the various types of HRTDs and delineate the spectrum of clinical expression and outcome.

**Patients and methods:** We reviewed the medical records of eighty children (48 males and 32 females) seen over an eight years period from (sep.2004-may2012) at children welfare teaching hospital.

**Results:** The distribution of patients according to HRTD was as follows: (56.25%) proximal RTA (pRTA), (30 %) distal renal tubular acidosis (dRTA), (2.5%) type IV RTA, (10%) Bartter's syndrome and (1.25%) Gitelman syndrome. Age at diagnosis ranged between 1 month and 16 years. Overall, consanguinity rate was as high as 85%. Rate of affected siblings was 58.75%. Failure to thrive was common symptoms in all our patients' with HRTDs. Renal failure was found in (24.4%) of patients with pRTA and 25% of patients with dRTA.

Hearing loss was present only in patients with dRTA (20.8%). Convulsions were noted in (37.7 %) of patients with pRTA, (16.6 %) patients with dRTA and the patient with Gitelman syndrome. Nephrocalcinosis were more common in dRTA patients (79.16%).

**Conclusions:** The high rate of consanguineous mating is likely to produce many heritable disorders including HRTDs by increasing the knowledge on demographic, clinical, and laboratory features of this rare disease group may serve to increase our current knowledge on this disease group making early diagnosis and life-saving treatment possible.

**Key words:** Hereditary tubular disorders, children, Iraq.

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## Introduction:

Multiple and complex functions of the renal tubule in regulating water, electrolyte, and mineral homeostasis make it prone to numerous genetic abnormalities resulting in malfunction. The phenotypic expression depends on the mode of interference with the normal physiology of the segment affected. (1)

In this study, we aimed to review single Iraqi centre experience with the various types of renal tubular disorders, identifying the demographic and main clinical features in these Patients admitted to Children welfare teaching hospital /Baghdad Medical City.

## Patients and Methods

We reviewed the medical records of children with hereditary renal tubular disorders (HRTDs) who were diagnosed in pediatric department of children welfare teaching hospital in the period from September 2004 to may 2012 .This hospital is a tertiary care centre, and receives referred patients from all parts of Iraq.

Records comprising HRTDs causing acid–base abnormalities and hypo/hyperkalemia, i.e., proximal renal tubular acidosis (pRTA), renal Fanconi syndrome, distal renal tubular acidosis (dRTA) ,type IV RTA, Bartter's syndrome, and Gitelman's syndrome, were included in the study.Data from patients with nephrogenic diabetes insipidus, idiopathic hypercalciuria, cystinuria, and other stone diseases such as hyperoxaluria were not included in the study, since they do not cause acid–base abnormality and hypo/ hyperkalemia.

Metabolic acidosis was defined as low serum HCO3 - concentration and pH below 7.35; metabolic alkalosis was defined as high serum HCO3 - concentration and pH above 7.45, accompanied with appropriate respiratory compensation. (2)

Diagnosis was made on the basis of clinical evaluation and laboratory studies including blood chemistry, electrolytes, blood and urine pH, urine electrolytes, metabolic evaluation, and renal imaging. Failure to thrive, polyurea, polydypsia, dehydration episodes, and electrolyte imbalance in infancy were regarded as the non specific clinical criteria for most HRTDs. The specific diagnostic criteria were as follows: for dRTA, hyperchloremic metabolic acidosis with hypokalemia, hypercalciuria, nephrocalcinosis, and inability to lower urinary pH below 5.5 in the face of spontaneous acidemia; for isolated pRTA, hyperchloremic metabolic acidosis with normal to slightly

low serum potassium level and the ability to lower urinary pH below 5.5 in the face of spontaneous acidemia or after acid load; for renal Fanconi syndrome, pRTA with excessive urinary losses of glucose, protein, phosphate, and amino acids;

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for cystinosis, renal Fanconi syndrome along with cystine crystals in cornea ,for type IV RTA, hyperchloremic metabolic acidosis with hyperkalemia and the ability to lower urinary pH below 5.5 in the face of spontaneous acidemia (3,4); for Bartter's syndrome, hypochloremic hypokalemic metabolic alkalosis with excessive urinary loss of calcium and chloride; and for Gitelman's syndrome, hyperchloremic metabolic alkalosis with hypocalciuria and hypomagnesemia presenting with tetany (5,6).

Clinical and laboratory findings such as serum chemistry, serum and urine pH, serum HCO3, urine analysis, urine calcium, urine protein, creatinine excretion, total phosphate reabsorption (TPR), metabolic tests, imaging studies, and follow-up data were recorded. The diagnosis of HRTD was made only when secondary factors causing tubulary dysfunction (i.e., diuretic use, cystic fibrosis, vitamin D Intoxication, obstructive uropathy, etc.)were excluded. The long follow-up period of tubular disorders also guided the diagnosis of HRTD in some patients. Data were extracted retrospectively from patients' files.

Statistics: Social science (SPSS) version17.0 was used for data analysis. Data are expressed as median (min–max) for quantitative variable and percentages for qualitative variables.

**Results:**

Eighty patients admitted to children welfare teaching hospital were diagnosed as having HRTD during the period from sep. 2004- may 2012

Demographic data (Table 1,2):

The study included eighty patients (48 boys, 32 girls), male/female ratio 1.5:1 .The distribution of the patients was as follows: 45 (56.25%) had renal Fanconi syndrome of whom 31 (38.75%) had cystinosis and 9 (11.25%) isolated pRTA, 24(30%) patients were had dRTA, 2 (2.5%) type IV RTA, 8 (10%) Bartter's syndrome, and 1 (1.25%) Gitelman's syndrome.

Age at diagnosis varied between 1 month and 16 years. Consanguinity rate was 85%, and the rate of affected siblings was 58.75%.

Clinical presentation and associated symptoms in (table 3) Although lack of appetite, and vomiting could be considered as non specific presenting symptoms but it was found as important presenting symptoms in most of our patients except the patient with Gitelman syndrome, followed by polyurea and polydypsia which was also a common presenting symptom in our patients except the patient with Gitelman syndrome as shown in table (3).

Failure to thrive was also common in this study, it was found in (93%) of patients with pRTA, (87.5%) of patients with dRTA, (87.5%) of patients with Bartter syndrome patients, but not found in the only one patient with Gitelman syndrome diagnosed in this study.

Eighteen patients (22.5%) had renal failure. Regarding those patients with pRTA 11/45 (24.4%) patient had renal failure, 9/45(20%) patients were with Nephropathic cystinosis, 1/45(2.22%) patient with unclassified Fanconi syndrome, and 1/45(2.22%) patient with Wilson disease.

Rickets was more common in pRTA in 41patients (91.1%), followed by type IV RTA (50%) and dRTA (37.7%). only one patient with Bartter syndrome (12.5%) had rickets.

Nephrocalcinosis was common in dRTA (79.16%), followed by Bartter's syndrome (37.5%) and only (4.44%) pRTA patients.

Ophthalmopathology was found in (35.5%) patients with pRTA and they were all cases of cystinosis as precipitated cystine crystals in cornea.

Hearing loss was found in only (20.8%) of patients with dRTA

Convulsions were noted in (37.7 %) of patients with pRTA, (16.6 %) of patients with dRTA and the patient with Gitelman syndrome.

In regard to Bartter's and Gitelman's syndromes, there were far more patients with Bartter's syndrome than Gitelman's syndrome (7 versus 1).

The Case with Gitelman's syndrome was a 7 years old female with normal growth, she complained from recurrent muscle cramps .Therapy was directed at correcting hypokalemia and hypomagnesaemia with supplemental potassium and magnesium.

**Table (1): Demographic features of patients with various hereditary renal tubular disorders**

| | pRTA | dRTA | Type 4RTA | Bartter's syndrome | Gitelman's syndrome | total |
|---|---|---|---|---|---|---|
| Patient number (%) | 45(56.25) | 24(30) | 2(2.5) | 8(10) | 1(1.25) | 80(100) |
| Gender (F/M) | 16/27 | 11/12 | 2/5 | 2/4 | 1/0 | 32/48 |
| Age at diagnosis, median (months); (min–max) | 24(2- 96) | 31(7- 72) | 36(5- 60) | 20(1- 38) | 48 | 12(1-96) |
| Consanguinity (%) | 90.6 | 82.6 | 71.4 | 66.6 | 100 | 85 |
| Family history (%) | 69.7 | 56.5 | 28.5 | 33.3 | - | 58.75 |

**Table (2): Relative frequency of different types of proximal renal tubular acidosis (pRTA) diagnosed in 45 patients seen at children welfare teaching hospital-Baghdad (2004-2012)**

| diagnosis | Patients No. (%) |
|---|---|
| Cystinosis | 31(38.75) |
| isolated pRTA | 9(11.25) |
| Galactosemia | 2(2.5) |
| Tyrosinemia | 1(1.25) |
| Gitelman syndrome | 1(1.25) |
| Glycogen storage disease | 1(1.25) |
| total | 45(100) |

**Table (3): Associated symptoms and complications of patients with various hereditary renal tubular disorders**

| Signs symptoms (%) | pRTA | dRTA | Type 4RTA | Bartter's syndrome | Gitelman's syndrome |
|---|---|---|---|---|---|
| Lack of appetite | 41/45(91.1) | 21/24(87.5) | 2/2(100) | 5/8(62.5) | - |
| Vomiting | 32/45(71.1) | 17/24(70.8) | ½(50) | 6/8(75) | - |
| polyurea | 37/45(82.2) | 19/24(79.16) | 2/2(100) | 6/8(75) | 100 |
| polydypsia | 36/45(80) | 19/24(79.16) | 2/2(100) | 5/8(62.5) | 100 |
| growth retardation | 42/45(93.3) | 21/24(87.5) | 2/2(100) | 7/8(87.5) | - |
| Rickets | 41/45(91.1) | 9/24(37.5) | ½(50) | 1/8(12.5) | - |
| Seizure | 17/45(37.7) | 4/24 (16.6) | - | - | 100 |
| Renal failure | 11/45(24.4) | 6/24(25) | - | 1/8(12.5) | - |
| Deafness | - | 5/24(20.8) | - | - | - |
| Ophthalmopathology | 16/45(35.5) | - | - | - | - |
| Nephrocalcinosis | 2/45(4.44) | 19/24(79.16) | - | 3/8(37.5) | - |

PRTA proximal renal tubular acidosis, dRTA distal renal tubular acidosis

**Discussion**

The renal tubules play an important role in fluid and electrolyte homeostasis. Tubular dysfunction should be considered in all children with failure to thrive, polyurea,refractory rickets, hypokalemia and metabolic acidosis. (7) Most of patients in this study presented with these symptoms so Careful clinical and laboratory evaluation is essential in these conditions for diagnosis and specific management.

Most tubular disorders have autosomal recessive inheritance characteristics, in This study group, consanguinity rate was 85% and the rate of affected siblings was 58.75%. More, undiagnosed patients may be there because we have a high consanguineous mating in Iraq, which can produce many patients with heritable disorders including HRTDs.

Failure to thrive found in most of the evaluated HRTDs (80–90% of patients), which may reflect late diagnosis and subsequent late commencement of treatment. Late diagnosis can be due to lack of awareness of HRTDs among general physicians and lack of diagnostic facilities, especially for the underlying metabolic diseases. Proximal RTA( Fanconi syndrome ),was the most frequent disorder encountered in the patients reviewed in this series, while a study done in Jordan they found distal RTA to be the most common form of referred patients to their centre.(8) Fanconi syndrome considered to be a general defect in the function of the proximal tubules cystinosis was the most common cause of Fanconi syndrome in this study. Other disorders that lead to renal Fanconi in this study were, isolated PRTA, galactossemia, Hepatorenal tyrosinemia (tyrosinemia type I) and Glycogen storage disease type I. The results were similar to that mentioned in literature (9) In this study group, 25 /80 (31.25%) patient had renal failure from mild renal insufficiency to end-stage renal failure (GFR \25 ml/1.73 m2). Nephropathic cystinosis was the most common cause leading to renal failure among HRTDs forming 18/31(58.06%), which might be due to insufficient specific cystagon treatment and insufficient follow-up. Renal failure was also observed in dRTA 6/24(25%) and Bartter's syndrome 1/8(1.25%), renal failure was secondary to nephrocalcinosis

and nephrolithiasis in these patients. Rickets in this study was common in patients with Fanconi and dRTA and this could be related to insufficient and late commencement of alkali treatment could be the cause (10). In regards to dRTA, and deafness, mutations in the ATP6V1B1 gene, encoding the B1 subunit, result in autosomal recessive distal RTA associated with nerve deafness. ATP6V1B1 is expressed in the cochlea and the endolymphatic sac, where the H+-ATPase pump likely plays an important physiological role to maintain the endolymph pH at 7.4. The late development of hearing loss in some patients with distal RTA linked to ATP6V0A4 mutations might be related with inappropriate sustained control of acidosis (10). Convulsions were seen in 17/45(37.7%) patients with pRTA and 4/24 (16.6%) patients with dRTA .Convulsions might be due to underlying electrolyte imbalance and/or secondary to severe vomiting and may be reversible with proper fluid and electrolyte treatment. Also in the only one diagnosed patient with Gitelman syndrome secondary to hypomagnesaemia. Bartter syndrome derived from a mutation to the NKCC2 (sodium potassium chloride cotransporter 2) found in the thick ascending limb of the loop of Henle . Classic Bartter's syndrome is usually diagnosed in childhood or adolescence (11) In this study 8/80(10%) patients diagnosed as Bartter all were classical variant, Gitelman syndrome was formerly considered a subset of Bartter syndrome until the distinct genetic and molecular bases of these disorders were identified. Gitelman syndrome (GS), also referred to as familial hypokalemia-hypomagnesemia, is characterized by hypokalemic metabolic alkalosis in combination with significant hypomagnesemia and low urinary calcium excretion. GS is transmitted as an autosomal recessive trait. Mutations in the solute carrier family12, member 3 gene, SLC12A3, which encodes the thiazide-sensitive NaCl cotransporter (NCC), are found in the majority of GS patients. In a small minority of GS patients, mutations in the CLCNKB gene, encoding the chloride channel ClC-Kb have been identified. (11) Diagnosis is based on the clinical symptoms and biochemical abnormalities (hypokalemia, metabolic alkalosis, hypomagnesemia and hypocalciuria). Bartter syndrome (especially type III) is the most important genetic disorder to consider in the differential diagnosis of GS. In the majority of cases, symptoms do not appear before the age of six years and the disease is usually diagnosed during adolescence or adulthood. (11, 12).In this study one female a 7 years old with hypocalciurea, hypomagnesemia diagnosed as (Gitelman syndrome).

**Conclusion:**

We conclude that, the high rate of consanguineous mating is likely to produce many heritable disorders including HRTDs, increasing knowledge on demographic, clinical, and laboratory features of this rare disease group may serve to increase our current knowledge on this disease group making early diagnosis and life-saving treatment possible.

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