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Original Article

Congenital and Hereditary Renal Diseases in the Cairo Kidney Center: Review of the Presenting Symptoms and Outcome - Any Place for Screening?

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Abstract

Objectives: The aim of this study was to determine the prevalence of various congenital and hereditary renal diseases in patients attending at the Cairo Kidney Center.

Methods: The files of 104 patients diagnosed as congenital or hereditary renal conditions were analyzed. There were 89 adult patients, and 15 children, less than 18 years. The youngest patient was 2 years and the oldest 72 years old.

Results: There were 39 patients suffering from autosomal dominant polycystic kidney disease (ADPKD), 25 patients presenting with different congenital anomalies, 11 patients with obstructive uropathy, 6 patients with Alport's syndrome, and 23 with variable other conditions. Of these 104 patients, 53 were in renal failure, 29 because of ADPKD, and 24 due to other congenital or hereditary conditions.

The study evaluated the presence of a family history of a similar condition, the absence of family history, or an unknown family history. A positive family history for ADPKD was found in 14 patients, yet only one patient from these families presented to screen for ADPKD. In one patient renal failure was diagnosed when she sought medical advice for intrauterine fetal death. She was twenty years old and had urinary incontinence since early childhood.

Conclusions: The study highlights the poor awareness of the families and their treating doctors of the importance of early detection and treatment of congenital and hereditary renal diseases.

The elucidation of the degree of awareness, in families with hereditary renal diseases and their treating doctors, is of great importance for early detection of renal conditions and improving the outcome.

INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is a common disorder, occurring in approximately 1 in every 400 to 1000 live births[1,2]. It is estimated that less than one-half of these cases will be diagnosed during the patient's lifetime, as the disease is often clinically silent[1]. Most families with ADPKD have an abnormality on chromosome 16 (in what has been called the PKD1 locus) that is tightly linked to the alpha-globin gene locus[3,4]. The remaining patients have a different defect[3,5] that in some cases involves a gene on chromosome 4[6]. Cysts occur later in non-PKD1 disease as does end-stage renal disease (mean age 69 versus 57 years in PKD1)[3].

The diagnosis of ADPKD is somewhat difficult to establish when children of an affected parent are screened for the disease, both for genetic counseling and for possible early therapy. Cysts as small as 1 to 1.5 cm in diameter can be detected by ultrasonography and 0.5 cm by CT scanning[3,7]. The optimal definition of a positive radiologic screening is uncertain. Standard criteria in patients with a family history of ADPKD required bilateral involvement with a total of at least 3 to 5 cysts[3,7]; cysts may also be seen in other organs[8]. Thus a positive test according to Ravine et al. (1994)[9], requires:

1. In patients younger than 30 years of age, at least two cysts (unilateral or bilateral).

Simple renal cysts are uncommon in these patients and are rarely multiple or bilateral.

2. In patients aged 30 to 59, at least two cysts in each kidney.
3. In patients over 60, four or more cysts in each kidney to minimize false positive results due to multiple simple cysts which are relatively common in these patients[5,10].

With the PKD1 abnormality, the probability of a positive ultrasonogram in the 50% of children who have the disease is estimated to be 8% below the age of 10 and increases to virtually 100% by the age of 30[3,10].

An additional issue is screening patients with ADPKD for the presence of an occult cerebral aneurysm, since a rupture aneurysm can lead to irreversible neurologic damage or death[7].

The second major group of patients in this study, is the group of congenital anatomic anomalies. Antenatal diagnosis of urologic conditions is becoming more frequent though not yet routine. Many of the congenital urologic anomalies have a familial tendency, so that fetal screening in a family with an affected member is recommended. On the other hand, there are many external physical features associated with variable urologic anatomic anomalies. Looking for these features in the neonatal period as possible indicators of renal anomalies is advised. Of the numerous external indicators, three are very important to look for: Hypospadias, single umbilical artery and preauricular pits.

1. Hypospadias: One study found that 12% of children with hypospadias screened by IVP and voiding cystourethrogram, had urinary tract disorders that ultimately required surgical intervention[11].
2. Single umbilical artery is present in 0.2 to 1.0% of births, occurring more frequently in twins and premature infants. In one report 30% of asymptomatic children with single umbilical artery had an abnormal IVP; two of these seven children required surgical intervention[12], in another study using renal ultrasound in children with single umbilical artery; 7.1% had significant renal abnormalities, mostly related to vesico-ureteric reflux[13].
3. Preauricular pits are present in 1% of white, 5% of black and 10% of Asian children. These lesions are definitely associated with renal anomalies when they are part of the autosomal dominant branchio-oto-renal (BOR) syndrome[14].

SUBJECTS AND METHODS

Two thousand files of patients were obtained randomly from the archives. Files of patients presenting with conditions other than renal were discarded. From the files related to renal conditions, only files of congenital or heredofamilial conditions were studied.

The files were searched for features in the natal period as possibly indicating renal anomalies. Of the numerous external indicators, three are very important to look for: hypospadias, single umbilical artery and preauricular pits.

All data were tabulated and analyzed.

RESULTS:

Table (1): Patients and Conditions

	Total no.	Males	Females
ADPKD	39	23	16
Congenital anatomic anomalies	25	15	10
Obstructive uropathy	11	8	3
Alport	6	4	2
Miscellaneous	4	1	3
Multicystic kidney	4	1	3
Incontinence	3		3
Essential hypertension	3	2	1
Hereditary nephritis	2	1	1
IgA nephropathy	2	1	1
Renal Tubular Acidosis	2	1	1
Metabolic stones	2	1	1
Reflux nephropathy	1	1	
TOTAL	104	59	45

CLINICAL DATA OF PATIENTS:

RF=renal failure , M= male, F= female, Y= yes, N= no, P= present, U= unknown, Nve= negative, Hturia=hematuria, Ptnuria=proteinuria, DX=dialysis, TX=transplantation

Table (2): ADPKD (autosomal dominant polycystic kidney disease)

code no.	age	sex	R.F.	Hturia	Ptnuria	Hyper-tension	Stones	DX	TX	Family history	Clinical presentation
23317	55	F	N	N	N	N	Y	N	N	U	Urinary tract infection
5566	42	M	Y	N	Y	Y	Y	N	N	U	Fatiguability
5563	54	M	Y	N	N	Y	N	N	N	U	Fatiguability
5107	44	M	Y	Y	N	Y	N	Y	N	P	Hematuria
1721	44	M	N	N	N	Y	Y	N	N	P	Hemospermia
1549	64	F	Y	N	N	Y	N	Y	N	U	Fatiguability
25946	65	F	Y	N	N	N	Y	Y	N	P	Fatiguability
22474	53	F	Y	N	N	Y	N	N	N	U	Hypertension
22558	45	M	N	N	N	Y	Y	N	N	U	Hypertension
5317	57	M	Y	Y	Y	Y	N	Y	N	P	Hypertension
5478	40	M	Y	Y	Y	Y	N	N	N	P	Fatiguability
5172	51	M	Y	Y	N	N	Y	N	N	P	Fatiguability
5192	39	M	Y	N	N	Y	N	N	N	P	Stone formation
23907	31	F	N	N	N	Y	N	N	N	U	Spontaneous abortion
23992	59	F	Y	Y	N	Y	N	N	N	U	Hturia & hypertension
23267	35	M	Y	Y	Y	Y	N	N	N	U	Renal failure
1061	27	M	Y	Y	Y	Y	N	Y	Y	U	Hypertension
23198	39	M	N	N	N	Y	N	N	N	U	Hypertension
23167	54	M	Y	Y	N	Y	N	Y	N	U	Renal failure
23388	50	M	Y	Y	N	Y	N	Y	N	U	Fatiguability
23293	51	M	N	Y	Y	Y	N	N	N	U	Pain and hemorrhage
23274	39	M	Y	N	N	Y	Y	N	N	Nve	Pain
23632	27	M	N	N	N	Y	Y	N	N	P	Hypertension
23629	42	M	Y	N	N	Y	Y	Y	N	Nve	Hypertension at 35 yr
22235	60	F	Y	N	N	Y	N	N	N	U	Weakness
22085	76	M	Y	N	N	Y	N	N	N	U	Fatiguability
22130	34	F	N	N	N	Y	N	N	N	Nve	Hypertension
2272	50	F	Y	N	N	Y	N	N	N	P	Hypertension at 31yr
2594	24	F	N	N	N	Y	Y	N	N	U	Urinary tract infection
2128	40	F	Y	Y	Y	Y	N	N	N	P	Pain and abortion
3085	34	F	F	N	N	Y	Y	N	N	P	US done for pregnancy
3026	40	F	N	N	N	Y	N	N	N	P	Hypertension
2855	38	F	Y	N	N	Y	N	N	N	U	Hypertension
2777	40	F	Y	N	N	Y	N	N	N	P	Hypertension
5383	40	M	Y	Y	Y	Y	N	N	N	U	Hypertension
22130	34	F	N	N	N	Y	N	N	N	Nve	Hypertension
5189	36	M	Y	Y	N	N	N	Y	N	P	Renal failure
5527	45	M	Y	N	N	N	Y	N	N	U	Hypertension
5511	62	M	Y	N	N	Y	Y	N	N	U	Hypertension

d- congenital small kidney(s):

code no.	age	sex	RF	Hturia	Ptnuria	Hyper-tension	Deafness	DX	TX	Family history	Clinical presentation
22500	58	M	mild	N	mild	Y	N	Y	N	N	Hypertension, bilateral
23832	48	M	N	N	N	Y	N	N	N	N	Hypertension, bilateral
5225	44	F	Y	N	N	Y	N	Y	N	N	Hypertension, bilateral
3234	56	F	Y	N	N	Y	N	Y	N	N	Loin aches, dysuria, gout 40 yr duration, unilateral
5129	16	M	N	N	N	Y	N	N	N	N	Headaches, bladder stone at 2 yr associated with medullary sponge left kidney and hypoplastic right kidney

e- variable anatomic anomalies:

26046	64	M	N	N	Y	N	N	N	N	N	Horseshoe, malrotation
23079	12	F	N	N	N	N	N	N	N	N	Horseshoe, infection
5390	21	M	N	Y	Y	Y	Y	N	N	N	Malrotation of left kidney, stones, hydronephrosis contracted, compensatory hypertrophy of right kidney
5307	37	M	Y	N	N	Y	Y	N	N	N	Bilateral ventrally rotated kidneys, hydronephrosis
5487	38	M	N	N	Y	N	N	N	N	N	Duplex kidneys, casts proteinuria
24999	49	M	N	Y	Y	N	N	N	N	N	Retrocaval right ureter with calyceal back pressure
2596	35	F	N	N	N	N	N	N	N	N	Deaf mute, pain in loins, double ureters
22204	28	F	Y	N	N	Y	N	N	N	N	Congenital absence of left kidney, small right kidney echogenicity grade II

f- obstructive uropathy

code no.	age	sex	RF	Hturia	Ptnuria	Hyper-tension	Deafness	DX	TX	Family history	Clinical presentation
25100	23	F	Y	N	N	Y	N	Y	Y	N	Pelviureteric juncyion obstruction, presented with pain.
23359	16	M	N	N	N	N	N	N	N	N	Stricture urethra, presented with pain.
2988	32	F	N	N	N	N	Y	N	N	N	Congenital hydronephrosis, recurrent pyclonephritis, presentation abdominal pain
25948	45	F	N	N	N	N	Y	N	N	N	Stricture ureter, hydronephrosis, apin
22418	47	M	N	N	N	N	N	N	N	N	Left ureteric stricture, narrow urethral meatus, mild back pressure, presented with pain
5132	16	M	N	N	N	N	N	N	N	N	Stricture lower right ureter prcsented with pain
5437	24	M	N	N	N	N	N	N	N	N	Bladder neck obstruction, bilateral ureteric stricture, infertility.
5168	5	M	N	N	Y	N	N	N	N	N	Pelviureteric junction obstruction discovercd during investigations for nephrotic syndromc.
23932	39	M	Y	N	N	Y	N	N	N	N	Prcsented with renal failure due to bladder neck obstruction.
23801	2	M	N	Y	N	N	Y	N	N	N	Ureteric stricture, presented with pain.
1478	36	M	N	N	N	N	Y	N	N	N	Bilateral pelviureteric junction obstruction, infection and stones.

g- reflux nephropathy

23346	20	M	Y	N	Y	Y	N	N	N	N	Urinary tract infection scarred both kidneys

Table (5): METABOLIC STONES

code no.	age	sex	RF	Hturia	Ptnuria	Hyper-tension	Stones	DX	TX	Family history	Clinical presentation
22134	10	M	N	Y	N	N	Y	N	N	P	Pain, hydronephrosis
22068	5	F	N	Y	N	N	Y	N	N	N	Hematuria at 3 m and infection

Table (6): INCONTINENCE

code no.	age	sex	RF	Hturia	Ptnuria	Hyper-tension	Stones	DX	TX	Family history	Clinical presentation
22153	12	F	N	N	N	N	N	N	N	N	Incontinence
23223	14	F	N	N	N	N	N	N	N	N	Incontinence
26111	26	F	Y	N	N	Y	N	N	N	N	Fetal death

Table (7): MULTICYSTIC KIDNEY

code no.	age	sex	RF	Hturia	Ptnuria	Hyper-tension	Stones	DX	TX	Family history	Clinical presentation
5472	43	M	N	N	N	N	N	N	N	N	Neurotic symptoms
5199	49	M	Y	Y	N	Y	N	N	N	N	Acute glomerulonephritis
2594	24	F	N	N	N	Y	Y	N	N	N	Pain, stone, infection, abortion

Table (8): IgA NEPHROPATHY

code no.	age	sex	RF	Hturia	Ptnuria	Hyper-tension	Stones	DX	TX	Family history	Clinical presentation
25497	33	F	N	Y	Y	N	N	N	N	N	Hematuria
5617	25	M	N	Y	N	Y	N	N	N	N	Hematuria

Table (9): RENAL TUBULAR ACIDOSIS

code no.	age	sex	RF	Hturia	Ptnuria	Hyper-tension	Stones	DX	TX	Family history	Clinical presentation
24917	32	F	N	N	N	Y	Y	N	N	N	Stone formation
22078	54	F	Y	N	N	Y	N	N	N	N	Fatiguability

Table (10): HEREDITARY NEPHRITIS

code no.	age	sex	RF	Hturia	Ptnuria	Hyper-tension	Stones	DX	TX	Family history	Clinical presentation
257555	35	M	Y	Y	Y	Y	N	Y	Y	P	Renal failure
22128	24	M	Y	N	Y	Y	N	N	N	N	Check-up for albuminuria

Table (11): MISCELLANEOUS

a- essential hypertension

code no.	age	sex	RF	Hturia	Ptnuria	Hyper-tension	Stones	DX	TX	Family history	Clinical presentation
5300	32	M	Y	Y	N	Y	N	N	N	N	Hypertension, blood pressure never normal, biopsy showed mem-branous nephropathy with severe interstitial lesion.
1229	49	F	Y	N	N	Y	N	N	N	N	Recurrent urinary tract infection
23647	30	M	N	Y	N	Y	Y	N	N	N	Dark urine, stone

b-others

25952	33	F	Y	N	13 g	N	N	N	N	N	FMF, loin pain
5134	46	M	Y	N	N	Y	Y	N	N	N	Hypertriglyceridemia
23050	47	F	N	Y	N	N	N	N	N	N	Multiple hemangio-mata, vascular impre-ssion at PUJ, without obstruction, hemangio-mata also in the liver, spleen, bladder, sponge kidney, stones infection.
22178	16	F	Y	N	Y	Y	N	N	N	N	FMF

DISCUSSION

The files of one hundred and four patients fulfilling the criteria of selection were included in the study. Thirty-nine patients had ADPKD, (Tables 1, 2), 23 males and 16 females. The youngest patient was 24 years old, a female presenting with urinary tract infection. She was also hypertensive and had stones. The family history of ADPKD was unknown. The presentation was by urinary tract infection in 2 (5.12%) patients (both females), by fatiguability in 8 (20.5%) patients. In all these patients renal failure was also found. Hematuria was the presentin sign in 1 (2.56%) patient who also had renal failure. Hematuria, occurs at some time in the course in 35 to 50% of patients with ADPKD and may be the presenting symptom of the disease[2,15]. Hemospermia was the presenting sign also in 1 (2.56%) of the patients presenting with hematuria. Hypertension was the presenting clinical complaint in 16 (41.02%) patients. Hypertension is a common early finding in ADPKD, occurring in 50 to 70% of cases before any significant reduction in glomerular filtration rate[16,17]. Stone formation was the presenting sign in one patient and was found in 12 other patients during the course of the disease (33.33%). Kidney stones occur in up to 20% of patients with ADPKD[8,18]. Pain was the presenting sign as a sole complaint in 1 (2.56%) patient, but was associated with hemorrhage in one patient and with abortion as presenting clinical manifestations of the disease in two other patients. Renal failure was the presenting sign in 3 (7.69%) patients, but was found in a total of 29 (71.79%) patients. ADPKD was found in a female patient when an ultrasound examination for pregnancy was done. This patient had a positive family history of ADPKD.

Fourteen patients (35.89%) had positive family history. None of these patients was diagnosed by screening. The family history was negative in 4 (10.25%) patients, and was unknown in 21 (53.84%) patients.

The diagnosis of ADPKD is easy to establish in overt disease. In some cases, however, the diagnosis of ADPKD is first suspected from ultrasonography performed for the evaluation of otherwise unexplained renal insufficiency or hematuria. This occurs most often in the 25 to 40 percent of new cases who have a negative family history[2]. This finding can represent either a new mutation[1], or, more commonly, a family with the late development of renal failure, in which affected patients die of other causes before the diagnosis is made[3].

One person with a positive family history came for screening and was found to have no disease.

Six patients 10 to 38 years old had Alport's disease, (Table 3), four males and two females. Five were in renal failure, one on dialysis, none transplanted and none presented for screening. Hereditary nephritis or Alport syndrome is inherited as an X-linked trait[19,20,21]. Autosomal recessive inheritence rarely occurs in hereditary nephritis, a setting in which women may be as severely affected as males[21,22]. The primary abnormality in almost all patients with hereditary nephritis appears to reside in the non-collagenous domain (NC1) of type IV collagen, involving the gene coding for the a-5 chain which is located on the X chromosome[20,21,23,24]. Autosomal recessive hereditary nephritis has been shown to involve the a-3 or a-4 chains, the genes for which are encoded head to head on chromosome 2[22]. Renal failure was the presenting sign in four patients (66.66%). In one of them it was

associated with thrombocytopenia. Concurrent platelet dysfunction is present in some families with autosomally transmitted disease[21]. In the other 2 (33.33%) patients hematuria was the presenting sign. Hematuria begins by age five in boys, but may not be diagnosed until adulthood unless the patient is screened because of an affected family member. End-stage renal disease usually occurs in males between the ages of 16 and 35, but the course is more indolent in some families with renal failure being delayed until age 45 to 60. This variability in clinical course may result in part from different mutations in the a-5 gene; affected males with a gene deletion may have more severe disease (both renal and extrarenal) than those with a lesser alteration such as point mutation[21,23,24]. A positive family history was present in two patients (33.33%), but in the other four patients the family history for Alport's disease was unknown.

Thirty seven patients presented with variable congenital anatomic anomalies, (Table 4).

Double or multiple renal arteries (Table 4 a) was found in five patients. They were all young males, they all presented with hypertension and one of them was in renal failure. Three patients had ***renal artery stenosis***, (Table 4 b), two males and one female. They all presented with hypertension. In one patient renal artery stenosis was associated with multiple arteries. None was in renal failure.

Ptosed kidney, (Table 4 c), was found in five patients, four females and one male. In four patients it was the right kidney that was ptosed in one patient ptosis was bilateral. They all presented with pain, except the patient with bilateral ptosed kidneys. Stones were found in one patient, and infection in another patient. Congenital small kidneys (Table 4 d) was diagnosed in five patients, three males and two females. Three patients had bilateral hypoplastic kidneys. In one patient the unilateral hypoplastic kidney was associated with a contralateral medullary sponge kidney with stones. All patients were hypertensive. Two had renal failure and one had mild impairment of renal functions. Eleven patients had variable congenital anomalies, (Table 4 e), horseshoe in two, malrotation in two. In one of these two patients hydronephrosis was also found and renal failure too, duplex system in one, retro-caval right ureter in one with back pressure and renal failure, double ureters in one and congenital absence of one kidney associated with congenitally small kidney in another. Two were in renal failure. Three were hypertensive, four were proteinuric and two were hematuric.

Obstructive uropathy, (Table 4 f), was found in eleven patients, 8 males and 3 females. The obstruction was at the pelviureteric junction in three patients in one of whom it was bilateral. Renal failure was present in one patient. Ureteric stricture was found in four patients and bladder neck obstruction in two patients. In one it ended in renal failure, and one patient presented with urethral obstruction.

Lastly one patient presented with reflux nephropathy, (Table 4 g). The diagnosis was made at the age of 20 years when the patient presented with scarred kidneys and renal failure. The true incidence of vesico-ureteric reflux is not known since most patients diagnosed present with urinary tract infection, whereas others present with vesicoureteric reflux alone and being silent for a long time remain undetected. Up to 30-50% of children with UTI will have vesicoureteric reflux, and

as many as one third of them will have reflux nephropathy[25]. The incidence of reflux nephropathy as a cause of ESRD has been reported to be 10%[26]. Thus although the incidence viewed in relation to the pediatric population at large is low, RN constitutes a significant number of patients in end-stage renal disease programs. Only one patient out of 104 patients was diagnosed as reflux nephropathy. Cases presenting with obstruction where vesico-ureteric reflux could be associated were classified under obstruction. On the other hand, patients presenting with UTI where VUR could not be related to congenital vesico-ureteric reflux were not included in the study. This could explain the very low number of patients diagnosed as reflux nephropathy in this work.

Two patients presented with metabolic stones, (Table 5). They were 10 and 5 years respectively. One patient had a positive family history for metabolic stones. The presentation was by pain and hydronephrosis in one and by hematuria at the age of 3 months in the other patient.

Three patients presented with urinary incontinence, (Table 6), dating since birth. They were all females. One patient sought medical advice for fetal death. She was in renal failure.

Multicystic kidneys, (Table 7), was diagnosed in three patients. In one patient it was associated with acute glomerulonephritis and renal failure. In another patient it was associated with pain, stone and infection. Two patients were hypertensive and one was in renal failure.

IgA nephropathy, (Table 8), was diagnosed in two patients one male and one female. The presentation was by hematuria in the two patients. One patient also had proteinuria but was not hypertensive while the other was. None were in renal failure. The family history was negative in both patients.

Renal tubular acidosis, (Table 9), was diagnosed in two patients. They were two female patients. Both were hypertensive, one was in renal failure, the other had renal stones.

Hereditary nephritis, (Table 10), other than Alport was diagnosed in two male patients 35 and 24 years of age. They were both in renal failure. One had a positive family history.

Miscellaneous conditions, (Table 11), were present in seven patients. Three had essential hypertension, (Table 11 a), two males and one female. Their ages ranged from 30 to 49 years. Two were in renal failure. Two patients had familial mediterranean fever, (Table 11 b). Both were females and both were in renal failure. They were 33 and 16 years old respectively.

One male patient had hypertriglyceridemia, (Table 11 b) hypertension, stones and renal failure. He was 46 years old. The last patient had multiple hemangiomata, (Table 11 b). She presented with hematuria, and had hemangiomata in almost all her organs. She was not hypertensive, she had renal stones and urinary tract infection.

Thus, a recommendation to screen families with hereditary and familial renal diseases, and a complete evaluation of conditions known to have a long term impact on renal function must be voiced. Antenatal screening for families with known congenital anomalies, and neonatal screening for the same families as well as those presenting with specific physical features hypospadias, single umbilical artery and preauricular pits, as well as any other congenital anomaly, should be done.

This study has showed that in 7 patients the ultimate outcome of renal failure could have been prevented, had a proper screening been done since early years. On the other hand, ESRD could have been delayed and complications reduced in 14 patients with positive family for ADPKD, if early screening was done to the families. In other words, the renal functions could have been preserved in approximately 20% of patients included in this study, with all that this figure represents with regards to the quality of life of the patients, and the burden of health expenses on the state and the families.

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