Congenital malformations of the urinary tract: progression to chronic renal disease

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ABSTRACT

Introduction. Congenital nephrourological abnormalities (CAKUT) are a particularly relevant group of diseases due to their high prevalence and the fact they are the main cause of chronic renal disease (CRD) in the pediatric population. Our objective was to determine the characteristics and prevalence of CAKUT in our setting, while identifying the factors associated with the occurrence of renal damage.

Materials and methods. A retrospective, descriptive, analytical, cross-sectional study of patients seen in the Pediatric Nephrology Department of a third-level hospital from January 1 to December 31, 2018 was carried out. Epidemiological, clinical, and analytical variables were assessed, and potential risk factors associated with CRD were searched for.

Results. The study involved 685 patients with 827 kidney units affected by CAKUT with a mean age of 9.98 ± 5.12 years. 62.2% were male, and the mean follow-up period after diagnosis was 9.95 ± 5.09 years. 58.8% were non-obstructive dilations, followed by renal dysplasia, obstructive dilations, and number and position abnormalities. The most frequent malformation was vesicoureteral reflux (VUR). The most commonly affected side was the left (47.5%). 55% of the diagnoses were prenatal. 172 patients underwent surgery. The initially chosen treatment for VUR was endourological. Overall re-intervention rate was 20%. Of the total number of patients, glomerular filtration rate was analyzed in 383, 95 (24.8%) of whom had CRD (86% in stage 2). Male sex, bilaterality, and proteinuria were risk factors associated with CRD.

Conclusions. Knowledge of the epidemiological and clinical characteristics of children with CAKUT and the factors associated with CRD helps to individualize the clinical follow-up of these patients, thus customizing diagnostic tests and healthcare resources.

KEY WORDS: CAKUT; Glomerular filtration rate; Chronic renal disease (CRD).

MALFORMACIONES CONGÉNITAS DEL TRACTO URINARIO (CAKUT): EVOLUCIÓN A ENFERMEDAD RENAL CRÓNICA

RESUMEN

Introducción. Las anomalías nefrourológicas congénitas (CAKUT), constituyen un grupo de enfermedades de gran relevancia por su alta prevalencia y por ser la principal causa de enfermedad renal crónica (ERC) en la población pediátrica. Nuestro objetivo es conocer las características y la prevalencia de CAKUT en nuestro medio, identificando los factores asociados a la aparición de daño renal.

Material y métodos. Estudio retrospectivo, descriptivo, analítico y transversal, que incluyó los pacientes atendidos en la consulta de Nefrología Pediátrica de un hospital de tercer nivel desde el 1 de enero al 31 de diciembre de 2018. Se analizaron variables epidemiológicas, clínicas y analíticas, y se buscaron posibles factores de riesgo asociados a ERC.

Resultados. Se incluyeron 685 pacientes con 827 unidades renales con CAKUT con una edad media de 9,98 ± 5,12 años. El 62,2% fueron varones y el seguimiento medio desde el diagnóstico fue de 9,95 ± 5,09 años. El 58,8% fueron dilataciones no obstructivas, seguido por displasia renal, dilataciones obstructivas y anomalías de número y posición. La malformación más frecuente fue el reflujo vesicoureteral (RVU). El lado más afectado fue el izquierdo (47,5%). El 55% de los diagnósticos fueron prenatales. Fueron intervenidos 172 pacientes. El tratamiento inicial de elección en el RVU fue endourológico. La tasa de reintervención global alcanzó el 20%. Del total de pacientes, se pudo analizar el filtrado glomerular en 383 pacientes, de los cuales 95 (24,8%) tenían ERC (86% en estadio 2). El sexo masculino, la bilateralidad y la proteinuria fueron factores de riesgo asociados a la ERC.

Conclusiones. El conocimiento de las características epidemiológicas y clínicas de los niños con CAKUT y de los factores asociados a la ERC ayuda a individualizar el seguimiento clínico de estos pacientes adecuando las pruebas diagnósticas y los recursos sanitarios.

PALABRAS CLAVE: CAKUT; Tasa de filtración glomerular; Enfermedad renal crónica (ERC).

INTRODUCTION

Congenital nephrourological abnormalities are known as CAKUT (Congenital Abnormalities of the Kidney and

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Urinary Tract) in the international literature. They have a high prevalence and are the most frequent cause of CRD in childhood (playing a decisive role in 30-50% of cases)[1]. They occur in 0.3-1.3 per 1000 live newborns[2].

Etiology is multifactorial in most cases. Genetic (approx. 10%), maternal, mechanical, and environmental factors have been described[2]. The genes involved include *HNF1β* and *PAX2*.

A large number of entities caused by **abnormal embryological development of the urinary tract** are included as CAKUT. Inadequate interaction between the ureteral bud and the metanephric blastema can lead to dysplastic kidneys if contact is poor, and to stenosis of the ureteropelvic junction if the junction is hypoplastic. It can also cause alterations in the shape, size, and position of the renal parenchyma[3]. They can occur in isolation or in the context of a syndromic disorder. The most common are those with dilation of the urinary tract.

Prenatal ultrasonography (from week 20) has allowed for early diagnosis and prognostic assessment[4]. Other imaging tests include voiding cystography (in suspected vesicoureteral reflux or VUR) and nuclear medicine tests – renal scintigraphy with dimercaptosuccinic acid (DMSA), Tc^{99m} (gold standard technique for the diagnosis of renal damage), and MAG3 Tc^{99m} diuretic renogram (if obstruction is suspected).

Renal survival varies significantly depending on the cause and the presence of risk factors for renal damage progression.

The main objective of our study was to determine the characteristics and prevalence of CAKUT in our setting, while identifying the risk factors associated with the development of CRD in this population.

Table I. Distribution of congenital abnormalities of kidney and urinary tract.

Pathology	*Prevalence in absolute values (% of total malformations)*
1. Obstructive dilatation	74 (8.9%)
• UPS	54 (6.5%)
• VUS	13 (1.5%)
• PUV	7 (0.8%)
2. Non-obstructive dilatation	487 (58.8%)
• VUR	320 (38.7%)
• Primary megaureter	23 (2.8%)
• Ectasis	
- Simple	17 (2.1%)
- Hydronephrosis	108 (13.1)
- Ureterocele	19 (2.3%)
3. Dysplasia	89 (10.6%)
• Multicystic renal dysplasia	69 (8.3%)
• Others: renal dysplasia	20 (2.4%)
4. Number abnormalities	70 (8.5%)
• Agenesis	66 (8%)
• Supernumerary kidney	4 (0.5%)
5. Size abnormalities: hypoplasia	27 (3.3%)
6. Position abnormalities	66 (7.9%)
• Ectopia	33 (4%)
• Horseshoe kidney	25 (3%)
• Malrotation	7 (0.8%)
• Others: ptosis	1 (0.1%)
7. Others	14 (1.7%)

UPS: ureteropelvic stenosis; VUS: vesicoureteral stenosis; PUV: posterior urethral valves; VUR: vesicoureteral reflux.

MATERIALS AND METHODS

A retrospective, cross-sectional, descriptive, analytical study was carried out. CAKUT patients seen at the Pediatric Nephrology Department of a third-level hospital from January 1 to December 31, 2018 were included. Patients with cystic disease and nephronophthisis complex were excluded, since they require a different diagnostic and therapeutic approach. Double isolated ureteropelvic system was regarded as a normality variant.

Demographic, analytical, and clinical variables were recorded, and 7 diagnostic groups were defined – they are featured in the results section (Table I). Only the data from the clinical visit that contained the most complete information on the variables under study was recorded.

As for treatment, conservative treatment was considered to be: micturition and bowel movement measurements, dietary and physical exercise recommendations, antibiotic prophylaxis, antiproteinuric treatment, or any other medical treatment for CRD. Surgical treatment was considered to be any conventional or endoscopic surgery of the urinary system.

Risk factors associated with renal damage included history of low weight at birth, prematurity, malformation in both kidneys (bilateral CAKUT), and obesity. Birth weight and prematurity were defined according to the World Health Organization (WHO)'s classifications, with preterm newborns being those born before completing the 37^{th} week of gestation, and low weight newborns (LBW) being those weighting less than 2,500 grams at birth. Body Mass Index (BMI) was calculated using the Endocrinoped application (Spanish reference charts 2010), expressed in kg/m^2, and compared with normal standards for children of the same age using percentiles and standard deviation (SD). Obesity was established when the BMI presented a >95 percentile.

Glomerular filtration rate (GFR) was estimated using the modified Schwartz formula (2009): **GFR (ml/min/1.73 m²) = Length or height (cm) × K constant/Serum creatinine** (K of 0.45 in <1 year, 0.413 in >1

Table II. KDIGO 2012 classification. Glomerular filtration rate (ml/min/1.73 m²).

G1	Normal or high	GFR ≥ 90
G2	Slightly low	GFR = 60-89
G3a	Slightly-moderately low	GFR = 45-59
G3b	Moderately-severely low	GFR = 30-44
G5	Renal failure	GFR < 15

Source: Kidney Disease: Improving Global Outcomes (KDIGO) CRD-MBD Update Work Group KDIGO 2017 clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of chronic renal disease-mineral and bone disorder (CRD-MBD). Kidney Int Suppl. 2017; 7: 1-59.

year). CRD was considered a >G1 stage (according to the KDIGO 2012 classification)[5] (Table II).

The presence of proteinuria, high blood pressure (HBP), cicatricial nephropathy, and history of urinary tract infection (UTI) were considered factors for renal damage progression. Proteinuria was quantified as the protein/creatinine ratio, with >0.2 mg/mg in children >2 years, and 0.4 mg/mg in children <2 years being considered positive. Blood pressure (BP) was measured during the clinical visit with an automated oscillometric device using standardized methods according to the 2016 European Guidelines[6]. SBP (systolic blood pressure) and/or DBP (diastolic blood pressure) ≥95th percentile were considered to be HBP (high blood pressure).

The presence of renal scars was assessed in those patients who had undergone renal scintigraphy or diuretic renogram. The Goldraich classification[7] of renal damage on renal scintigraphy was used, with cicatricle nephropathy being defined as the presence of any type of renal scars.

Having suffered a febrile urinary tract infection, as recorded in the patient's medical record, was considered as a history of urinary tract infection.

For the CRD prevalence study, only the group of patients where serum creatinine measurement and GFR estimation were available was considered. In this group, a comparison of variables was conducted according to the presence or absence of CRD.

Statistical analysis was performed using the SPSS 20.0 software (SPSS Inc., Chicago, IL, USA). Normality of the variables was assumed for the sample size, and parametric statistical tests were used, with statistical significance being established at $p < 0.05$. Differences in continuous independent variables were analyzed using the Student's t-test, whereas ANOVA was used for continuous and qualitative non-dichotomous variables. Proportions in categorical data between groups were analyzed using the Chi-squared test for qualitative variables. When the expected frequency (EF) was <5, Fisher's exact test was used. The Odds Ratio was calculated to quantify the association between two dichotomous variables.

RESULTS

From a total of 2717 appointments, CAKUT was identified in 827 kidneys in 685 patients. Age ranged from 3 months to 19.91 years, with a mean of 9.98 ± 5.12 years. 62.2% of patients were male, and mean follow-up period following diagnosis was 9.95 ± 5.09 years.

Non-obstructive dilations were the most numerous group (58.8% of cases), followed by renal dysplasia, obstructive dilations, and number and position abnormalities (Table I). Among the non-obstructive dilations, the most frequent malformation was VUR, which was present in almost 40% of the patients. 142 patients had more than one nephrourological malformation, with positional abnormalities occurring most commonly in association with other malformations (31.6%), followed by renal dysplasia (21.9%) and non-obstructive dilation (21.7%). Obstructive dilation (17.6%) and size (13.6%) and number (13%) abnormalities ($p < 0.05$) were less commonly associated with other abnormalities ($p < 0.05$).

The most commonly affected side was the left (47.5%), followed by the right (32.3%). Bilateral involvement was noted in 19.3% of cases.

In 29 cases (4.2%), the patients suffered from a specific polymalformative syndrome or genetic disorder. There was a clinically or genetically identifiable specific syndrome in 24 patients (some were chromosomopathies) and 5 genetic alterations. 7 of them were girls with a single kidney with OHVIRA syndrome, 3 with coloboma renal syndrome, 2 with Turner syndrome with horseshoe kidney, and 2 with Down syndrome.

Among the associated pathologies, the most common were neurological malformations (57 cases), followed by digestive malformations (32 cases). 35% of the patients had a nephrourological family history (FA) ($p = 0.4$).

In the group of patients as a whole, diagnosis was established at 13.79 ± 30.19 months (CI: 11.51-16.07) on average, with 55% being diagnosed prenatally, 27.2% in the first year of life, 10.4% at preschool age, and 8.2% over 5 years of age. There were significant differences in the age of diagnosis according to the underlying pathology. Diagnosis was established earlier in obstructive pathologies and dysplasias, and later in number abnormalities (Fig. 1). Excluding the prenatal diagnosis, the reason for diagnosis was the study of a urinary tract infection (26.7%) or an incidental finding (11.8% of cases). In non-obstructive dilations, the study of infection led to the diagnosis of CAKUT in 85.2% of cases. In the remaining diagnostic categories, it was an incidental finding ($p < 0.001$).

A first surgical procedure was performed in 172 patients. Obstructive pathologies required surgery in 92.6% of cases, vs. 23.3% in cases of non-obstructive dilatations, 15.7% in position abnormalities, 10.9% in dysplasia, 2.9% in patients with number abnormalities, and 0% in those with size abnormalities ($p < 0.001$).

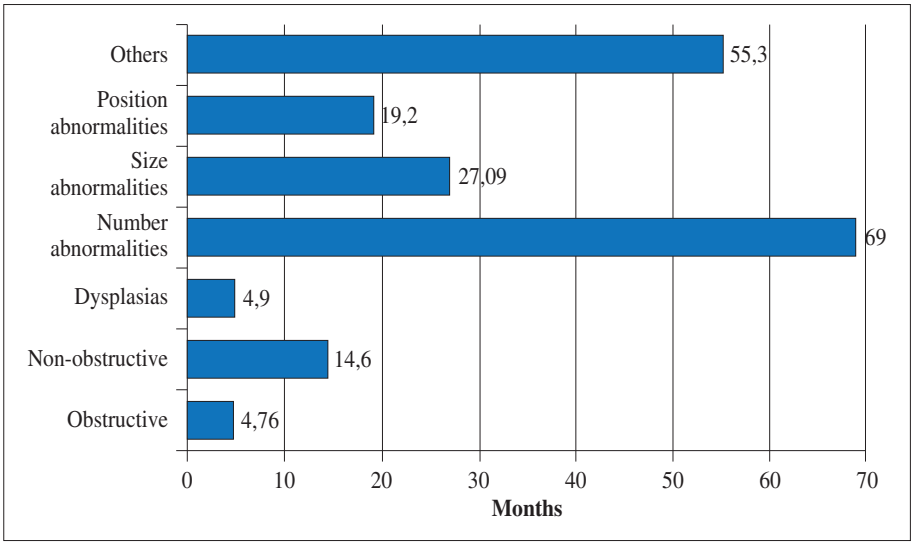

Figure 1. Diagnostic age of CAKUTs according to etiology.

Table III. Weight at birth and prevalence of low-weight and pre-term newborns in each etiology group.

	*Weight at birth in grams (mean ± SD)**	*Prevalence (% of the total of patients in each group)*	
		*LWNB***	*PTNB****
Obstruction	3380.88 ± 437.372	1.7%	7.9 %
Non-obstructive dilatation	3175.69 ± 553.533	8.6%	10.6%
Dysplasia	3332.54 ± 624.439	10.1%	5.7%
Number abnormalities	2986.05 ± 667.484	14.5%	10.9 %
Size abnormalities	2755.24 ± 864.712	33.2%	27.3%
Position abnormalities	2967.40 ± 567.221	12%	18.9 %

*LWNB: low-weight newborn; PTNB: pre-term newborn; *p < 0.001 for ANOVA; **p = 0.001 for Chi²; ***p = 0.007 for Chi².*

Regarding obstructive uropathies, 47 cases of ureteropelvic stenosis (UPS) required surgery. 51% of them underwent endoscopic dilation, 17 required pyeloplasty, 3 required bypass, and 3 required nephrectomy – the surgical technique was not recorded in one case. Nine vesicoureteral strictures (VUS) were operated on, 7 by endoscopic dilation, with one ureteral re-implantation and one bypass. Six cases of posterior ureteral valves (PUV) underwent surgery.

Regarding VUR, 86% of patients received endourological treatment (ureteral injection of Deflux® in 25 patients, Macroplastique® in 20 patients, and 9 unspecified). High grade VUR was present in 51%, medium grade in 25%, and low grade in 9%. In 9 cases, ureteral re-implantation was performed as the first surgical technique.

Some type of surgical bypass was carried out in 11 cases, in 6 of them due to complex uropathies associated with more than one obstructive pathology. 18 nephrectomies were conducted due to functional annulment of the kidney associated with high-grade VUR in 10 cases, 4 UPSs, and 4 cases of multicystic renal dysplasia.

Excluding those with a second lesion requiring surgery, 25 re-interventions were performed, with an overall re-intervention rate of 20.5%. Significant differences were noted for each technique ($p < 0.001$), from 36% for endoscopic treatment of VUR with Deflux® and Macroplastique®, to 6.6% for pyeloplasty, with 25% for endoscopic dilations and 11.7% for re-implantation. Of the patients with VUR in whom initial treatment with Deflux® and Macroplastique® failed, 73% had high-grade VUR.

Regarding the factors related to renal damage, weight at birth ranged from 925 to 5090 grams, with a mean of 3157.23 g ± 597.26. A total of 63 patients had low weight at birth (9.2%), with a total of 68 preterm newborns (9.9% of cases). There were significant differences according to the underlying pathology, both in weight at birth weight and in the relative frequencies of low weight at birth weight and prematurity, which were higher in patients with number, size, and position abnormalities (Table III).

Involvement was bilateral in 19.3% of the patients, as mentioned above.

Incidence of obesity in the series as a whole was 9.2%, with significant differences according to the different pathologies ($p = 0.004$). Obesity was more common in the group of patients with renal dysplasia (21.9%), followed

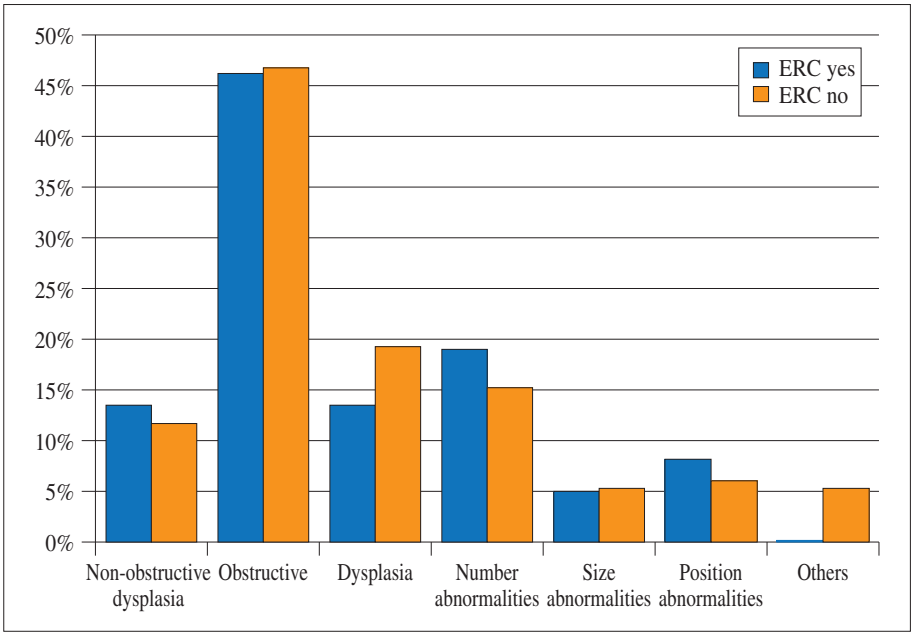

Figure 2. Distribution of baseline pathologies according to the occurrence or non-occurrence of chronic renal disease (CRD).

by obstructive pathologies (12.1%), number and position abnormalities (11.7% and 10.5%, respectively). It was less common in patients with non-obstructive nephrouropathies (5.9%) and with size abnormalities (4.5%).

A total of 85.3% of patients maintained normal BP at follow-up, with 7.7% of cases of normal/high blood pressure, and 7% of patients with high blood pressure. 0.7% of all patients (5 cases) required treatment with ACEI or ARA2. There were no differences in terms of HBP incidence between the pathology groups studied, but there were differences in disease progression time, which was significantly higher in the group of patients without HBP (10.3 ± 9.9 months [CI 9.9-10.7] vs. 5.1 ± 5 months [CI: 3.-6.5]; $p < 0.001$).

71.7% of patients had an isotope imaging/function test (67% renal scintigraphy with DMSA Tc^{99m} and 4.7% diuretic renogram MAG3 Tc^{99m}). 22.3% developed renal scars, the relative frequency being much higher in patients with non-obstructive dilations of the urinary tract. According to the Goldraich classification[7], we obtained 37.3% of type I cicatricial nephropathy, followed by 35.9% of type II, 26.1% of type III, and 0.7% of type IV.

To analyze progression to CRD, of the 685 patients who made up the study group, we selected those who had at least one blood creatinine measurement that allowed GFR to be calculated using the modified Schwartz formula. Thus, 383 patients were included, 95 of whom (24.8%) had CRD, 82 (86%) in stage 2, 11 in stage 3, and 2 in stage 4. The proportion of males was 77.9%, and male sex was considered a risk factor in this series (OR: 2.4; CI: 1.4-4.1). Although there were no differences regarding age at diagnosis between patients with and without CRD (mean age of 1.6 ± 3.1 in patients with CRD, and 1.1 ± 2.5 years in patients without CRD), patients with CRD were significantly older and, consequently, had a longer progression time (13.7 ± 4.6 years in patients with CRD, and 10.4 ± 4.6 years in patients without CRD. $P < 0.01$). There were no differences in the distribution of underlying pathologies according to the development or not of CRD (Fig. 2).

Neither were there any significant differences in the proportion of patients with prenatal diagnosis – which was 52.6% for patients with CRD, and 62.5% for patients without CRD ($p = 0.09$) –, nor can intrauterine diagnosis be considered a protective factor (OR: 0.67; CI: 042-1.06). Similarly, the presence of a family history of nephrourological disease, which occurred in 29% of patients with CRD and in 36% of patients with normal renal function ($p = 1.21$), was not a risk factor for CRD (OR 0.7; CI: 0.4-1.2).

The presence of at least one of the risk factors analyzed – prematurity, low weight at birth, obesity, and bilateral renal lesions, taken together – was more frequent in patients with CRD, but this association was not significant. Likewise, when individualized, although prematurity and low weight at birth were more common in patients with CRD and, surprisingly, obesity was more common in patients without CRD, none of these differences was significant. On the other hand, bilaterality was significantly more common in patients who developed CRD, and could be considered a risk factor.

With regard to other factors that could influence disease progression, other markers of actual or potential renal damage were analyzed, such as the presence of urinary tract infections, AHT, proteinuria, scars, and kidney and/or urinary tract surgery. While infections and scars were more common in patients without CRD, high blood pressure was

Table IV. Analysis of the risk factors assessed for CRD.

	CRD				
Prematurity	14.3%	13.1%	0.33	1.4	0.7-2.9
Low weight at birth	11.6%	10.5%	0.8	1.1	0.5-2.5
Male sex	77.9%	60.2%	<0.05	2.4	1.4-4.1
Obesity	7.4%	13.1%	0.14	0.5	0.2-1.2
Bilaterality	25.3%	15.6%	<0.05	1.8	1.1-2.2
Risk factors	38.9%	34.1%	0.38	1.2	0.8-1.9
Other renal damage markers as CRD risk factors					
Infections	30.5	37.5	0.13	0.7	0.4-1.2
Hypertension	15.3	12.8	0.34	0.8	0.5-1.5
Proteinuria	16.3	5	<0.001	4.6	2.1-10.5
Renal scars	20	277.4	0.09	0.7	0.4-1.2
Surgery	33.7	28.5	0.2	1.3	0.8-2.1

CRD: chronic renal disease.

more common in patients with CRD. However, none of these associations was significant. In contrast, there was a significant association between the presence of proteinuria and CRD, which means it can be considered a risk factor associated with CRD. These results are summarized in table IV.

DISCUSSION

CAKUTs are highly prevalent, accounting for 20-30% of prenatally detected malformations. Furthermore, they are the most common cause of CRD in children, accounting for 40-50% of those requiring renal replacement therapy worldwide[4]. They are a heterogeneous and difficult-to-pigeonhole group of pathologies with great clinical variability, ranging from asymptomatic cases to cases that are incompatible with life. It was therefore important to know the clinical and epidemiological characteristics of children with CAKUT in our setting, as well as the prevalence of CRD and the differentiating characteristics in children with renal damage.

Due to their high prevalence, they are a frequent reason for visits to specialized centers, requiring periodic clinical follow-up, especially those with a higher risk of developing renal damage, those with urinary tract infections, or those who may require surgical treatment.

The high number of study patients shows the frequency and great relevance of this pathology in our setting. Follow-up is prolonged until adulthood, especially in cases at risk of renal damage and those with CRD. Thus, mean age and follow-up time of the children in the study was around ten years, with a maximum age of 19 years.

CAKUTs were more common in males (62%), consistent with other studies[1], despite the fact that few epidemiological data has been published to date.

The most common malformation was non-obstructive dilation, consistent with other series[8]. According to clinical protocols, after postnatal confirmation of moderate or severe urinary dilation, voiding cystography was performed and VUR was diagnosed. Indeed, VUR was the most common pathology in this diagnostic group and in the series as a whole, accounting for two thirds of the total. Almost half the VUR cases were high grade, that is, refluxes that caused dilation of the urinary tract, possibly due to the fact that most of them were diagnosed with hydronephrosis.

More than one nephrourological malformation was associated with 20% of the patients – mainly renal ectopia and horseshoe kidney classified as positional abnormalities, as well as renal dysplasias. The frequent association with other malformations in our series with VUR and hydronephrosis makes cystography advisable in this type of malformation. Furthermore, they are associated with other non-renal congenital abnormalities in 30% of cases[9], and the association of CAKUT and non-renal abnormalities is present in more than 200 syndromes. In our series, the proportion of association with other malformations was 29%, but a specific syndrome or genetic mutation was only identified in 5% of the patients. This is much lower than the percentage reported in the literature, probably because we did not routinely study mutations in the panel of genes associated with CAKUT, with the molecular genetic study being reserved for those cases with a specific clinical suspicion. 35% of patients had some family history of nephrourological disease (20-50% in the literature)[10]. This data highlights the probable involvement of genetic and epigenetic factors[4].

Improvements in prenatal ultrasonography and its systematic use have contributed to the early detection of CAKUTs, most of which are diagnosed prenatally (55% of the cases in our series) or in the first year of life (27% of our patients)[11]. Prenatal diagnosis was more frequent

in obstructive dilations and dysplasias – mostly multicystic renal dysplasia – with respect to number abnormalities, thus highlighting the sensitivity of prenatal ultrasonography in assessing hydronephrosis and renal cysts[2].

Left CAKUTs were more prevalent, accounting for almost half of the cases, and involvement was bilateral in up to 19.3% of cases. Bilaterality proved to be one of the most important markers of renal function prognosis[2].

In general, treatment possibilities include interruption of pregnancy (in bilateral renal agenesis), fetal surgery (in severe obstructions), conservative treatment (most commonly), and surgical treatment (in obstructive pathologies).

In our series, a total of 172 patients underwent initial surgery, which represents 25% of the total. The pathology that required surgery most frequently was obstructive, where virtually all cases underwent surgery. Given that obstructive pathology can cause irreversible renal damage, which worsens the renal prognosis of these patients, early surgical treatment is a priority.

In percentage terms, CAKUTs represent the main cause of CRD in all pediatric series[12]. In European and North American series, we observed that the percentage of chronic renal disease caused by CAKUTs ranges between 48 and 59%[3]. In Spain, this percentage is 56% in stage 2 to 4 patients according to the data provided by the Spanish Pediatric Nephrology Society. In our series, the percentage of patients with CRD was 24.8%. However, this is biased because it was not possible to measure GFR in all study patients.

In our study, we also examined the prevalence of certain risk factors for renal damage, such as prematurity and low weight at birth. These conditions result in lower nephron endowment and therefore an increased risk of triggering the compensatory mechanism of hyperfiltration that eventually leads to proteinuria, high blood pressure, glomerular sclerosis, and progression to CRD. The frequency of these pathologies was significantly higher in patients with number, size, and position abnormalities, as described in one of the few series published on this aspect, which suggests that this association could be based on the alteration of the genes that jointly affect the development and growth of the kidneys and other organs[13].

The prevalence of obesity in our cohort was much lower than that of children in our region, where it is as high as 30%.

The incidence of normal-high BP and HBP was 14%, similar to that reported in the pediatric population as a whole, and no differences were found between the various malformations. It is conceivable that HBP is associated with renal damage and not with the type of CAKUT.

Many CAKUTs, especially non-obstructive dilatation of the urinary tract, are transient and progress satisfactorily towards recovery. However, some of them require surgical treatment to preserve renal function. Diagnostic tests and clinical follow-up of these children are aimed at identifying those who will benefit from such treatment, avoiding iatrogenesis in those who will have a satisfactory prognosis.

Follow-up reached adulthood in some cases, as we have mentioned, which allows us to better understand the natural course of the disease and the late onset of CRD.

We should point out that our center does not have a chronic renal replacement therapy program, so patients who develop terminal CRD are transferred to pursue follow-up in a referral center for dialysis and transplantation. This special characteristic should be taken into account in the study of patients with renal damage, since those who have progressed to advanced stages are not treated on a scheduled basis in the clinic. This represents a limitation to our study, which only includes those patients with stage 2 to 4 CRD according to the KDIGO 2012 guidelines[5].

Patients with CAKUT and CRD were compared with those with normal GFR. In the 383 (56%) patients studied (where GFR measurement was available), a similar percentage of boys was found, but with a significantly older mean age and longer follow-up times than the sample as a whole, possibly due to selection bias. The proportion of etiological diagnoses in this group of patients followed a pattern similar to that of the total sample, with non-obstructive dilation of the urinary tract as the most common pathology, followed by renal dysplasia.

A quarter of them had CRD (14% of all children with CAKUT), and most of them were classified as stage 2. Early stages of CRD are the most prevalent in the pediatric population with CAKUT, as shown in the data from the annual report of the Spanish registry. The clinical and epidemiological characteristics of children with CRD were similar to those with normal GFR. Male sex doubled the risk of CRD in contrast to other factors considered, such as prematurity, low weight at birth or obesity, UTIs, HBP, scars, and surgeries.

Proteinuria turned out to be the only modifiable risk factor associated with CRD in our series, so its treatment is essential in these patients. It is a factor recognized as a consequence of renal damage caused by the hyperfiltration mechanism, and at the same time, it is a renal progression factor.

In clinical practice, knowledge of the characteristics of children with CRD and the associated risk factors helps to identify high-risk patients or situations, and to adapt treatment and clinical follow-up.

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