Histopathological findings in children with idiopathic nephrotic syndrome in Honduras, 2016-2020

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Research Article

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Abstract

Background: Idiopathic nephrotic syndrome is the most common kidney disease in children, it is characterized by the presence of massive proteinuria, edema, hypoalbuminemia and hyperlipemia and can be caused by different histopathological subtypes.

Methodology: Descriptive cross-sectional observational study. Histopathological and clinical data were collected from 52 pediatric patients with idiopathic nephrotic syndrome who underwent USG-guided kidney biopsy in two third level hospitals in northwestern Honduras during January 2016 to December 2020. Convenience sampling was used; the data was exported to SPSS v.25 statistical program, where statistical analysis was performed. Descriptive statistics were used to obtain the frequencies and percentages of the categorical variables, and the median and the interquartile range (IQR) of the quantitative variables were obtained.

Results: the median age was 9 years [IQR, 3.0 - 12.0]; 55.8% were male. The clinical presentation of nephrotic syndrome in 34.6% of the cases was cortico-dependent nephrotic syndrome, followed by cortico-resistant nephrotic syndrome in 36.5%. The main subtype of glomerulopathy presented was the minimal change disease in 36.5%, followed by 28.8% corresponding to focal and segmental glomerulosclerosis.

Conclusions: In Honduras the real incidence of the different histopathological variations is unknown, therefore kidney biopsy becomes a fundamental tool to establish the diagnosis, treatment and prognosis of the disease.

Introduction

Idiopathic nephrotic syndrome (INS), the most common kidney disease in children, occurring in about 90% of cases [1], is characterized by the presence of massive proteinuria, generalized edema, hyperlipidemia and hypoalbuminemia [2]. It is caused by different histopathological subtypes; in low-income countries such as Honduras, the true incidence of the different variations is unknown, therefore kidney biopsy becomes a fundamental tool to establish the diagnosis, treatment, and prognosis of the disease.

The estimated annual incidence in the United States and Europe is 7/100,000 [3], due to the absence of national and hospital registries, epidemiological studies, as well as the presence of other challenges, such as the reduced number of specialists, lack of capacity to perform kidney biopsies and interpret histopathological findings, that result in the absence of capacity to perform kidney biopsies in hospitals of the public health system where the greatest number of patients occur, the lack of nephropathologist, makes it difficult to estimate cases at the national level; this problem is also present in other developing countries [1]. Most cases are concentrated in patients between 2 and 10 years of age, representing the

INS or primary group, while those under one year of age are attributable to a genetic cause [2]. The most frequent histopathology reported is minimal change disease (85%), followed by focal segmental glomerulosclerosis (FSGS); most cases of INS relapse for a considerable period of time from their first episode (80–90%), but have a good long-term prognosis, with the exception of steroid-resistant patients, where 50% of patients develop terminal chronic kidney disease at 5 years [1–2, 4–5]. Approximately 80–90% of children with INS respond to steroids, classifying them as corticosteroid-responsive INS [6].

In 1970, the ISKDC (*International Study of Kidney Disease in Children*) reported minimal change disease as the most frequent histological variation in kidney biopsies of children with INS, but subsequent research has shown significant changes in recent decades [7–9]. Response to steroid treatment varies by geographic region, depending on etiology, genetics, and underlying pathology [1]. The Gold Standard for diagnosis is the performance of a kidney biopsy, but its high cost and being an invasive procedure in children limits its frequency in developing countries, such as Honduras.

Most children with steroid-responsive INS have minimal change disease, whereas those with steroid-resistant INS have focal segmental glomerulosclerosis [10–11]. Recent studies in adults have reported an increase in the incidence of FSGS, unfortunately in the pediatric population in recent years, studies have focused on patients with cortico-dependence or frequent relapses, therefore the different histological variations in the clinical presentation of this disease may present differences or be underestimated [1]. Changes have also been demonstrated in the histological pattern of the disease, where FSGS and mesangioproliferative glomerulonephritis have become more common lesions, with a decrease in cases of minimal change disease. As minimal change disease is the most common subtype reported in studies, the standard of treatment in new-onset INS implies assuming minimal change disease and initiating treatment with steroids without biopsy, however, high resistance or relapses warrant the need for biopsy to identify histopathological etiology [10]. This may unnecessarily expose patients with steroid-resistant INS to adverse effects and could delay treatment with other therapies to which they are more likely to respond [11].

In Central America, there is a high incidence and prevalence of kidney diseases in advanced stages in the adult and pediatric population; and in most cases the cause is unknown, there is also no statistical data on the incidence of this disease, neither record of the most frequent clinical presentation and the histopathological lesions that cause it.

The purpose of this study is to perform clinicopathological correlation and to identify the most frequent histological lesions in the pediatric population with idiopathic nephrotic syndrome in which kidney biopsy was performed during the years 2016 to 2020. This study is unique since it is the first in describing the epidemiology of INS among Honduran children.

Methods

This study used a descriptive observational design with a cross-sectional time cut between 2016 and 2020, using retrospective collection of patient files from the Pediatric Nephrology service of the Hospital

Nor-Occidental Mario Catarino Rivas (HNMCR) and the Honduran Social Security Institute (IHSS), both tertiary level public care hospitals and the centers of greatest reference for the entire northwestern part of the country. Pediatric patients under 18 years of age with idiopathic nephrotic syndrome (INS) in their different clinical presentations were enrolled and underwent ultrasound-guided kidney biopsy.

Census-type convenience sampling was carried out, since all the records were available, taking the universe at the time of study as a sample. A total of 52 patients who met the inclusion criteria underwent ultrasound-guided kidney biopsy. The indications for kidney biopsy included: All patients between newborns and 18 years who presented cortico-dependence, cortico-resistance, frequent relapse, and also patients younger than 2 years and older than 10 years in their first episode were included, since these are also criteria to perform kidney biopsy in INS. Likewise, those patients who presented hypocomplementemia and nephrotic syndrome plus acute kidney failure were included. Cortico-sensitive patients were given a kidney biopsy when they presented the sum of an added variable such as: hematuria, arterial hypertension or altered normal function tests. Patients with secondary nephrotic syndrome were excluded from the study.

The INS was defined as the presence of proteinuria > 40mg/m2/h, hypoalbuminemia < 2.5g/dL and hypercholesterolemia > 200mg/dL. All patients were treated with Prednisone 60mg/m2/day for 4 to 6 weeks (maximum 80 mg/day). Response to treatment was classified according to ISKDC as: Cortico-sensitive: complete resolution of proteinuria before 8 weeks of treatment; Cortico-resistance: failure of response to treatment after 8 weeks of prednisone; Cortico-dependent: recurrence of proteinuria when the dose of corticosteroids is decreased or within two weeks of completing the treatment; frequent relapse: two or more episodes of proteinuria in a 6-month period after the initial response or 4 episodes in the 12-month period; Infant nephrotic syndrome: nephrotic syndrome which occurs between 3 and 12 months of age; Congenital nephrotic syndrome: nephrotic syndrome that occurs between NB and three months of age and nephrotic syndrome with hypocomplementemia: patients with C3 and C4 complement values lower than the acceptable ranges for their age.

To sample the kidney biopsy material, automatic firing guns are used that incorporate 16 Gauge echogenic needles, 3 renal cylinders were extracted, each cylinder is expected to contain a sample greater than 10 glomeruli, since samples less than that amount are not capable of detecting focal lesions, so a sample greater than 10 glomeruli per cast is considered adequate. All kidney biopsies were processed, cut, and stained with Hematoxylin-eosin, periodic acid Schiff and Masson's trichromic acid, methenamine silver, then examined by light microscopy and immunofluorescence (IF). Immunofluorescence staining was performed with antibodies and complement components that included IgG, IgM, IgA, C3, and C1q. No biopsy underwent electron microscopy since we do not have this diagnostic method in the country. All biopsies were interpreted and reported by the same nephropathologist, in the same laboratory during the five-year period.

Minimal change disease was defined by the absence of any abnormality on light microscopy. FSGS was characterized by the presence of at least one glomerulus showing an area of segmental sclerosis with or

without interstitial fibrosis and tubular atrophy. Diffuse mesangial hypercellularity (HMD) was defined by the presence of increased matrix and mesangial cell proliferation, more than four cells per mesangial area, in the absence of glomeruli with segmental sclerosis. Since several of the kidney biopsy criteria depend on the response to treatment, the patients were treated according to the KDIGO (Kidney Disease: Improving Global Outcomes) guidelines for the treatment of patients with idiopathic nephrotic syndrome. Kidney biopsies were performed prior to the start of corticosteroid treatment.

Sociodemographic and clinical variables associated with the clinical presentation of INS and glomerulopathy subtype included the patient's age (quantitative data), gender (male and female), presence of arterial hypertension (Yes/No), hematuria (Yes/No), edema (Yes/No), kidney test abnormalities (Yes/No), presence of immunofluorescence (Positive/Negative), presence of hypocomplementemia (Yes/ No).

For data collection, a form was created with the previously mentioned variables in Microsoft Excel (version 2016 for Windows; Microsoft). All data were exported to a comparison table in SPSS Software (Statistical Package for the Social Sciences) version 25.0, where the descriptive analysis was performed. Frequencies and percentages of the categorical variables were obtained, the median and interquartile ranges of the quantitative variables were found, and previously the Shapiro Wilk normality test was performed. This study was carried out in accordance with good clinical practices derived from the International Conference on Harmonization and the Declaration of Helsinki, in addition to complying with all current local laws and hospital permits, with the approval of the institutional ethics committee of the Universidad Catolica de Honduras with revision number CEI # EXP-2020-004.

Results

The study sample was made up of 52 pediatric patients with idiopathic nephrotic syndrome with kidney biopsy criteria. The 55.8% belonged to the male gender (29), the remaining 44.2% to the female gender (23), the median age was 9 years [IQR, 3.0–12.0] (Table 1).

The clinical presentation of the nephrotic syndrome in 36.5% corresponded to cortico-resistant nephrotic syndrome (19), 34.6% of the cases were cortico-dependent nephrotic syndrome (18), 21.2% had a steroid-sensitive clinical presentation (11), and 7.7% infant nephrotic syndrome (4). (Table 2)

According to the subtype of glomerulopathy presented, 36.5% corresponded to minimal change disease (19), 28.8% to focal and segmental glomerulosclerosis (15), 19.2% presented as diffuse mesangial hypercellularity (10), 13.5% as proliferative membranous glomerulonephritis (7), and 1.9% membranous as glomerulonephritis (*Graph 1*).

Regarding the clinical symptoms that the patients presented, in their totality they presented with edema, 30.8% had elevated kidney function tests (16), 25% presented arterial hypertension (10), 55.8% of the patients presented hematuria (29) (See Table 3). Regarding the complement, 81.1% of the patients were

normal, 17.3% of the cases presented hypocomplementemia (9), of which 7 were due to a decreased C3, one case to a decreased C4, and one patient presented a decrease in both supplements (Table 3).

67.3% of the patients who underwent immunofluorescence had negative results (n = 35), the remaining 30.8% were positive for at least one marker (16); of which 6 were only positive for IgM and the rest for IgM, IgG and C3 simultaneously. Immunofluorescence was not performed on one patient.

Table 1
Sociodemographic and clinical characteristics of the patient.

Characteristic	n (%)
Gender	29 (55,8)
Male	23 (44,2)
Female	9 (IQR, 3,0–12,0)
Age, mean [a]	3 (5,8)
Age groups	16 (30,8)
<12 months	14 (26,9)
1–5 years	19 (36,5)
6–10 years	13 (25,0)
> 11 years	52 (100,0)
Hypertension	29 (55,8)
Edema	16 (30,8)
Microscopic hematuria	9 (17,3)
Kidney Insufficiency	9 (17,3)
Interstitial fibrosis	16 (30,8)
Tubular atrophy	9 (17,)
Immunofluorescence (+)	
Hypocomplementemia	

[a] Interquartile range

Table 2
Clinical presentation of idiopathic nephrotic syndrome versus glomerulopathy subtype

Clinical presentation of idiopathic nephrotic syndrome	Glomerulopathy subtype					
	MCD	FSGN	MGN	MPGN	DMH	Total
Cortico resistant	2 (3,8)	8 (15,4)	0 (0,0)	6 (11,5)	3 (5,8)	19 (36,6)
Infant nephrotic syndrome	3 (5,8)	0 (0,0)	0 (0,0)	0 (0,0)	1 (1,9)	4 (7,7)
Cortico dependent nephrotic syndrome	8 (15,4)	3 (5,8)	1 (1,9)	1 (1,9)	5 (9,6)	18 (34,6)
Steroid sensitive nephrotic syndrome	6 (11,5)	4 (7,7)	0 (0,0)	0 (0,0)	1 (1,9)	11 (21,1)
Total	19 (36,5)	15 (28,8)	1 (1,9)	7 (13,5)	10 (19,2)	52 (100)

MCD = Minimal Changes Disease; FSGN = Focal Segmental Glomerulonephritis; MGN = Membranous glomerulonephritis; MPGN = Membranoproliferative glomerulonephritis; DMH = Diffuse Mesangial Hypercellularity

Table 3
Clinical and biochemical profile among different subtypes of glomerulopathies.

Clinical / biochemical characteristic	Glomerulopathy subtype					
	MCD	FSGN	MGN	MPGN	DMH	Total
Microscopic hematuria	7 (13,5)	10 (19,2)	0 (0,0)	6 (11,5)	6 (11,5)	29 (55,8)
Hypertension	3 (5,8)	3 (5,8)	0 (0,0)	4 (7,7)	3 (5,8)	13 (25,0)
Altered kidney function [a]	4 (7,7)	4 (7,7)	0 (0,0)	5 (9,6)	3 (5,8)	16 (30,8)

MCD = Minimal Changes Disease; FSGN = Focal Segmental Glomerulonephritis; MGN = Membranous glomerulonephritis; MPGN = Membranoproliferative glomerulonephritis; DMH = Diffuse Mesangial Hypercellularity

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Discussion

In our report, 52 patients with a diagnosis of idiopathic nephrotic syndrome and kidney biopsy criteria between the ages of 1 month and 18 years were evaluated, this would be the first pediatric report of

kidney histopathological findings in Honduras. Kidney biopsy is described as an invasive but safe procedure required to classify the different clinical spectrum of kidney disease in children, these findings are of vital importance to determine an accurate diagnosis and a long-term prognosis, and thus establish a therapy more effectively [12].

The median age of the study patients was 9 (IQR, 3.0–12.0) years, similar to that reported in pediatric populations in Latin America: Venezuela (11 years) [13], Colombia (11 years) [14] and Panama (8.3 years) [15], and slightly higher than that reported in Mexico (5.9 years) [16], also in East Asian and European countries similar ages are reported in Egyptians (9.2 years) (12), in Sudan (8.71 years) [17], Saudi Arabia (10.6 years) [18], India (7.9 years) [19], Pakistan (11.2 years) [20], Croatia (10 years) [7], other studies have revealed an earlier age at diagnosis [21].

The indication for kidney biopsy prevailed in the male gender (55.8%), similar to that reported in other studies [7, 12, 20, 22]. Of the total of cases studied, the most frequent indication for biopsy was cortico-resistant nephrotic syndrome, representing 36.5% of cases, followed by 34.6% cortico-dependent nephrotic syndrome, 21.2% sensitive to steroids, and 7.7% % as nephrotic syndrome of the infant. Arif MK et al. (2016), showed similar data in Tanzania with 48% cortico-resistant, 33.3% of cortico-sensitive children, and only 13.3% cortico-dependent [20], likewise, Bakr A, et al. (2014), reported 28.4% of cortico-resistant children [12]. These results are consistent with those reported in other countries following a similar pattern of presentation and differ slightly from other studies. For example, Ali A. (2008), reports different figures with a greater predominance of cortico-sensitive children representing 87% and 13% cortico-resistant [23], in Serbia the most frequent indication was cortico-dependent (32%), [24] differing from what was observed in this report.

In the last three decades, minimal change disease has been established as the most common cause of INS, with a prevalence that varies between 77–99% in different studies [25]. However, changes in histopathological patterns have been observed in recent years. The results show that minimal change disease is the most frequent histological variant in 36.5% of cases, however, it does not present the high percentages reported by other authors [25].

Focal and segmental glomerulosclerosis was identified as the second most frequent cause with 28.8% of cases, followed by diffuse mesangial hypercellularity (19.2%). In other series, FSGS is increasingly common in children with INS, ranking as the main cause [17, 19, 20, 26], which would warrant a kidney biopsy to establish a diagnosis and precise management even in places with scarce resources such as ours. The prevalence of FSGS could be explained by its behavior of complicating other glomerular injuries and its resistance to steroids with a poor subsequent prognosis [27]. The reason for the disparity between MCD and FSGS is uncertain, but it is attributed to demographic, environmental and genetic factors [28].

In this series, no patient with IgA nephropathy was reported, countries such as Morocco, Egypt and India also have no or low rates of IgA nephropathy [12, 29–30]. In countries of East Asia and Europe, IgA nephropathy is the most frequent histopathological diagnosis in kidney biopsies [7, 31–32]. International reports differ in the histopathological diagnosis between the predominance of one glomerulopathy over

another, attributable to geographical variation and racial predisposition and the different indications for kidney biopsy that were taken into account in each study; different histological methods for diagnosis must also be taken into consideration, and the use of different pathological classifications [7]. This study shows histological patterns that differ from what is reported in the international literature as the most frequent.

17.3% of the patients presented tubular atrophy and interstitial fibrosis, respectively, most of these presenting in the FSGS, which would demonstrate a chronicity of the disease and little response to steroid therapy. Therefore, these patients present an increased risk of progressing to chronic disease and developing more side effects [33].

Our study represents a sample of patients with INS with kidney biopsy criteria, defining the INS as the presence of proteinuria > 40mg/m2/h, hypoalbuminemia < 2.5g/dL and hypercholesterolemia > 200mg/dL; INS continues to be the main indication for kidney biopsy, agreeing with the majority of studies [34–35]. European countries such as Italy and England place proteinuria as the main indication [36], in Hong Kong systemic diseases rank first [37]. By comparing different studies, in different regions, we could demonstrate that the indications for kidney biopsy have changed in recent years.

The most important limitation of the study is its retrospective nature, limiting access to information and the lack of electron microscopy since this method is not available in Honduras and it is currently considered an essential component to describe glomerular pathology. There was no exclusion of cases, all biopsies performed from 2016–2020 were studied. This pediatric study is the first report of kidney histopathological findings in Honduras that will lay the foundations for future research in the country. These findings are important for the diagnosis, prognosis, and therapeutic approach in the clinical evaluation of Honduran children. The results belong to two second-level care hospitals, being the centers of greatest reference on the north coast of the country, but they are not representative of the total population, due to the selection bias, limiting the true emergence of kidney disease in Honduran children. Since the performance of a kidney biopsy in all children who present biopsy criteria depended on the consent of the parents and their economic condition to pay for it, it is not a procedure available within the public services of the country.

Conclusion

This study represents one of the first cases of histopathological findings in kidney biopsies of pediatric patients in Central America and the first in Honduras. It is vitally important to distinguish early the histopathological diagnosis of minimal change disease from other glomerulopathies in the INS, for the application of an effective therapy. A marked trend of predominance of subtypes other than MCD is seen in different populations, making the histopathological diagnosis crucial for the prognosis of the disease. In third world countries, such as ours, children with INS are managed with empirical treatment without having a histological diagnosis, and after a certain time of follow-up, the patient may develop resistance due to the change in the kidney histological pattern. Kidney biopsy in patients who meet criteria should be

performed from the first moment for a better selection of treatment, which would improve the quality of patient care.

Declarations

Competing interests

Conflict of Interest

The authors have no relevant financial or non-financial interests to disclose.

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Data availability statement

Patient's files and datasets used to support the findings of this study are restricted by the ethics committee of the "Universidad Catolica de Honduras" to protect the privacy of clinical data. Data are available to investigators who comply the criteria for access to confidential data under request to the ethics committee. Requests for access to these data should be directed to César Alas: cesar_alas10@hotmail.com.

Author's contributions

All authors contributed to the study conception, design and writing. Material preparation, data collection and analysis were performed by Rubén Galeas and César Alas-Pineda. The manuscript was written, edited and reviewed by Rubén Galeas, César Alas-Pineda and Kristhel Gaitán-Zambrano. All authors read and approved the final manuscript.

Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of the Universidad Catolica de Honduras with revision number CEI # EXP-2020-004.

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Figures

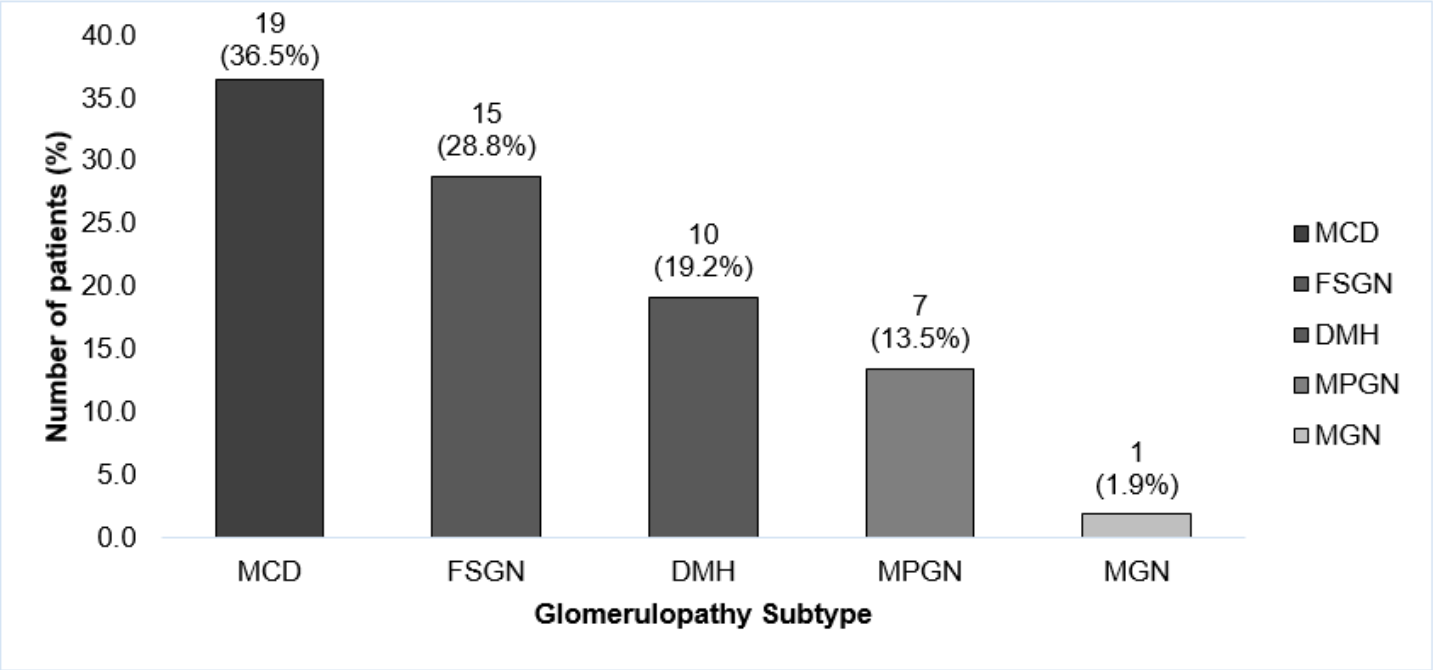

Figure 1

Subtype of glomerulopathy

MCD= Minimal Changes Disease; FSGN= Focal Segmental Glomerulonephritis; MGN= Membranous glomerulonephritis; MPGN= Membranoproliferative glomerulonephritis; DMH= Diffuse Mesangial Hypercellularity

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