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Spectrum of histopathological findings in pediatric renal biopsies; a five-year single center experience in Egypt

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ABSTRACT

Introduction: Medical renal diseases stand as one of the major health problems in pediatric age group considering its morbidity/mortality and the subsequent management plans.
Objectives: In this manuscript, the spectrum of histopathological patterns of medical nephropathic lesions in Egyptian pediatric patients over duration of five years is reported with clinical indications.
Patients and Methods: We conducted a retrospective study for analysis of our pathological reports of renal needle biopsies during the period from January 2014 until January 2019. One hundred and sixteen cases were included.
Results: The most commonly encountered pediatric renal pathology was minimal change disease (27.59%), followed by congenital glomerular diseases (22.41%), focal segmental glomerulosclerosis (12.93%), and thrombotic microangiopathy (7.76%). The most common clinical indication for biopsy was nephrotic syndrome (37.07%) followed by impaired renal functions with elevated serum creatinine (21.55%). In addition, we report very rare histological findings in few cases including infantile nephropathic cystinosis, Barakat syndrome and C3 glomerulopathy.
Conclusion: Minimal change disease and congenital glomerular diseases accounted for half of pediatric renal pathologies in the study population. The most common clinical indication for renal biopsy was nephrotic syndrome. Electron microscopic examination and genetic studies are mandatory for proper evaluation of pediatric nephropathies.

Implication for health policy/practice/research/medical education:
In this manuscript, we provide a brief report about the frequency and patterns of medical renal diseases in pediatric patients from a single center in Egypt over duration of five years. Rare histopathological findings are presented in few cases.

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Original Article

Introduction

The range of renal diseases in pediatric population is wide and variable from treatable conditions with benign outcome to life-threatening disorders (1). The prevalence and patterns of medical renal diseases in this age group are variable among different ethnic population. Data are published based on studies of renal biopsy specimens from different countries (2-9); however, those available from African/Arab countries are lacking with few published reports (10,11). Renal diseases, in particular those progressing to end-stage kidney disease (ESKD) have a well-established indirect impact on global morbidity and mortality by increasing the risks associated with cardiovascular diseases, diabetes mellitus, hypertension and various infections. Although pediatric ESKD patients constitute a minute proportion of the total ESKD population, they pose unique challenges to health care providers, who must address not only the primary renal disorder but also the systemic effects that may retard the patients' development (12). In general, the diagnostic approach of pediatric needle renal biopsy follows the same principles as it does for adults specimens; including assessment of adequacy and a systematic evaluation of the glomerular, tubulointerstitial and vascular components, followed by the use of ancillary studies such as immunohistochemistry and electron microscopy (13).

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Objectives

In this study, we report the relative frequency of pediatric nephropathies in a single center in Egypt based on histological diagnoses. Rare histopathological findings in few cases are highlighted (infantile nephropathic cystinosis, Fabry disease carrier with acute diffuse proliferative glomerulonephritis, Barakat syndrome and C3 glomerulopathy).

Patients and Methods

Study design

Between January 2014 and January 2019, a total of 116 needle renal biopsies from pediatric patients (aged up to 18 years old) were received at our nephropathology unit. Patients' data including age, gender, and other laboratory findings were obtained from the medical reports. The main presentation, biopsy indication and the current therapeutic regimen were recorded. Our standard protocol for material preparation includes submission of at least one core for light microscopic (LM) examination, one core for immunofluorescence (IF) study and 1 mm portions for electron microscopic (EM) examination for selected cases. Inadequate biopsies and patients with indeterminate end-stage pathological features were excluded from this study. In brief, the light microscope samples are fixed in buffered formalin, dehydrated in graded alcohols, cleared in xylene and embedded in paraffin using standard techniques. A set of slides is prepared from serial cuts (3 µ thick); stained with hematoxylin/eosin (H&E), Masson's trichrome (MT), periodic acid–Schiff reagent (PAS) and Jones methenamine silver (JMS). For IF study, the samples are immediately frozen in a cryostat then sections are cut at 5 µ thick, rinsed in a buffer and reacted with fluorescein-tagged polyclonal rabbit antihuman antibodies against IgG, IgA, IgM, C3, C4, C1q, fibrinogen, Kappa and Lambda light chains (Dako, Carpinteria, CA; Kent Laboratories, Bellingham, WA, USA). For samples failed for IF examination, salvage immunoperoxidase technique (IP) is performed; 3 µ thick sections from the paraffin blocks are prepared on charged glass slides, treated for antigen retrieval, and then treated with antibodies (against IgG, IgM, IgA and C3) using avidin biotin-peroxidase technique, 3,3'-Diaminobenzidine is utilized as a substrate and chromogen and hematoxylin is used as a counterstain. For transmission EM examination, tissue portions are fixed in glutaraldehyde, processed and embedded in epon, thick sections are prepared and stained with toluidine blue, thin sections are stained with uranyl acetate and lead citrate, placed on a grid for EM examination. The patients' histopathology reports were revised in order to document the following parameters; specimen nature (cortical/corticomedullary), percent of global sclerosis, glomerular lesions, tubulointerstitial lesions; tubular atrophy, interstitial inflammation and interstitial fibrosis were scored (0–3) as defined in the Banff schema, and the vascular lesions.

Statistical analysis

Data were handled using the GraphPad InStat computer software version 3.10 (GraphPad Software, Inc., La Jolla, CA, USA) and summarized using the mean and standard deviation for quantitative variables, whereas the frequency and percentages were used for the qualitative ones.

Results

This study included 116 cases, 68 males (58.62%) and 48 females (41.38%) with age range from four months to eighteen years (males 9.3±4.62, females 8.67 ± 4.68). Generalized edema was the most common presenting symptom (50.86%) (Figure 1), followed by hematuria (37.93%), growth retardation (6.03%) and dysuria (4.31%). One case of acute tubular injury was encountered presented with anuria (0.86%). The principle clinical indication for renal biopsy in our patients was as follows in a descending order (Figure 2); nephrotic syndrome (37.07%), followed by impaired kidney function with elevated serum creatinine (21.55%), recurrent hematuria (19.83%), persistent proteinuria with recurrent hematuria (11.21%), subnephrotic proteinuria (6.03%), congenital/infantile nephrosis (1.72%), persistent hematuria post-infectious glomerulonephritis (1.72%), and Fanconi syndrome (0.86%). The clinical laboratory findings are summarized in Table 1. Renal biopsy of our patients revealed the following characteristics (Figure 3); 1. Glomerular affection: (27.59%, n = 32) of our patients had minimal change disease (MCD). Congenital glomerular diseases ranked second (22.41%, n= 26): [(8.62%, n= 10) showed features of genetic abnormality of the GBM "not otherwise classified", hereditary nephritis features were found in (7.76%, n= 9), (3.45%, n= 4) had thin

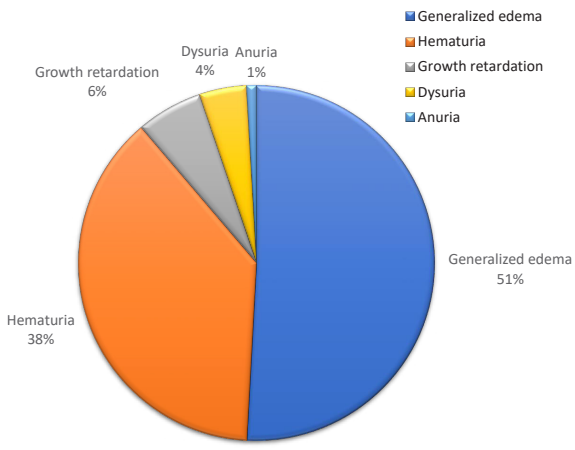

Figure 1. The main manifestations of renal disease in the study patients.

Table 1. The clinical laboratory findings of the patients[a,b]

Pathological diagnosis	sCr (mg/dL)	Proteinuria (g/d)	ASO (IU)	ANA (EU)	C3 (mg/dL)	C4 (mg/dL)	pANCA (+ve/-ve)	cANCA (+ve/-ve)
MCD (n= 32)	0.70 ± 0.23	7.45 ± 4.30	180.06 ± 111.04	10.26 ± 7.36	135.12 ± 23.18	26.77 ± 8.82	-	-
FSGS (n= 15)	2.37 ± 2.40	5.08 ± 3.90	199.13 ± 133.29	23.53 ± 10.63	160.33 ± 26.29	26.40 ± 10.93	-	-
Genetic GBM abnormality (unclassified) (n= 10)	0.44 ± 0.16	0.75 ± 0.80	148.00 ± 91.77	9.60 ± 8.21	151.80 ± 31.19	30.00 ± 10.33	-	-
Hereditary nephritis (n= 9)	0.74 ± 0.30	1.03 ± 0.93	138.67 ± 61.45	14.67 ± 8.72	139.65 ± 19.64	22.89 ± 9.44	-	-
TMA (n= 9)	4.18 ± 1.70	0.83 ± 0.37	195.78 ± 59.53	13.11 ± 8.67	121.56 ± 24.88	22.89 ± 12.85	-	-
CIN (n= 8)	4.74 ± 2.30	1.21 ± 0.33	250.00 ± 138.00	38.00 ± 18.58	116.00 ± 24.70	45.25 ± 14.85	-	-
ADPGN (n= 7)	2.29 ± 0.68	3.60 ± 3.39	778.00 ± 113.19	49.14 ± 17.20	42.86 ± 18.97	8.57 ± 4.86	-ve	-ve
MPGN (n= 5)	1.26 ± 0.11	2.44 ± 0.34	232.00 ± 90.11	46.80 ± 19.78	55.20 ± 19.68	7.20 ± 3.03	-ve	-ve
TBM (n= 4)	0.40 ± 0.08	0.11 ± 0.03	154.00 ± 22.80	11.00 ± 8.87	155.25 ± 18.39	36.00 ± 5.66	-	-
C3 GN (n= 4)	0.63 ± 0.13	1.24 ± 0.89	120 ± .16.33	19.00 ± 18.51	41.50 ± 18.14	40.00 ± 12.54	-	-
Membranous (n= 2)	1.00 ± 0.14	12.50 ± 6.36	155.00 ± 63.64	30.00 ± 28.28	100.00 ± 14.4	60.00 ± 21.21	-	-
IgA nephropathy (n= 2)	0.9 ± 0.14	2.30 ± 1.84	92.00 ± 39.60	-ve	70.00 ± 2.83	15.00 ± 7.07	-	-
Pyelonephritis (n= 2)	8.50 ± 2.12	1.40 ± 0.14	264.00 ± 33.94	-ve	141.00 ± 9.90	42.00 ± 8.49	-	-
CNS (n= 2)	0.90 ± 0.85	4.00 ± 1.41	72.00 ± 11.31	-ve	128.00 ± 5.66	20.00 ± 5.66	-	-
ATN (n= 1)	2.40	0.00	136.00	-ve	132.00	40.00	-	-
Amyloidosis (n= 1)	0.80	4.50	364.00	-ve	188.00	46.00	-	-
Barakat syndrome (n= 1)	1.50	0.60	289.00	-ve	164.00	24.00	-	-
Crescentic GN (n= 1)	12.00	2.00	212.00	-ve	148.00	36.00	+ve	-ve
Infantile cystinosis (n= 1)	0.40	0.15	64.00	-ve	172.00	78.00	-ve	-ve

[a] Values are presented as mean ± SD.
[b] (-): Not available/performed, (+ve): positive, (-ve): negative, (EU): ELISA units.
ADPGN: Acute diffuse proliferative glomerulonephritis, ANA: Antinuclear antibody, ASO: Anti-streptolysin O titer, ATN: Acute tubular necrosis, C3: Complement component C3, C3GN: C3 glomerulonephritis, C4: Complement component C4, cANCA: Cytoplasmic antineutrophil cytoplasmic antibody, CIN: Chronic interstitial nephritis, CNS: Congenital nephrotic syndrome, FSGS: Focal segmental glomerulosclerosis, MCD: Minimal change disease MPGN: Membranoproliferative glomerulonephritis, pANCA: Perinuclear antineutrophil cytoplasmic antibody, TBM: Thin basement membrane disease, TMA: Thrombotic microangiopathy, sCr: serum creatinine.

basement membrane (TBM) disease, (1.72%, n= 2) had features of congenital nephrotic syndrome (CNS), and one case (0.86%) had infantile nephropathic cystinosis]. The rest of encountered glomerular pathologies were; (12.93%, n= 15) had focal segmental glomerulosclerosis (FSGS), (6.03%, n= 7) had acute diffuse proliferative glomerulonephritis (ADPGN), (4.31%, n= 5) had membranoproliferative glomerulonephritis (MPGN), (3.45%, n= 4) had C3 glomerulonephritis (C3GN),

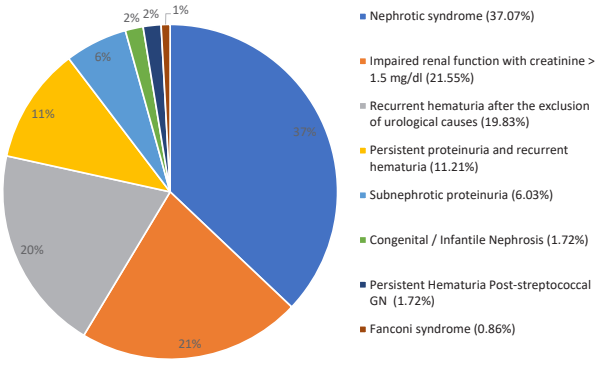

Figure 2. The principle clinical indication for renal biopsy at time of presentation.

(1.72%, n= 2) had membranous nephropathy, (1.72%, n= 2) had IgA nephropathy, one case (0.86%) known to have familial Mediterranean fever had glomerular amyloidosis and crescentic glomerulonephritis was seen in one case (0.86%). Glomerulonephritis was primary in (83.16%) of cases and secondary in (16.84%), 2. Tubulointerstitial affection: (6.90%, n=8) of our patients had chronic interstitial nephritis (CIN), (1.72%, n= 2) had pyelonephritis, acute tubular necrosis (ATN) was found in one case (0.86%), and one case (0.86%) known to have Barakat syndrome showed mild interstitial fibrosis associated with unusual pattern of arterial/arteriolar vasculopathy, 3. Vascular affection: (7.76%, n=9) had thrombotic microangiopathy (TMA); six of which were in acute phase and the rest showed variable features of chronicity. Additional histopathological findings are summarized in Table 2. Rare histopathological findings were encountered in few cases deserve mentioning. The infantile nephropathic cystinosis case (Figures 4 and 5), showed numerous dark lysosomal inclusions in the podocytes, endothelial cells, tubular epithelial cells and interstitial cells. One case presented with acute diffuse

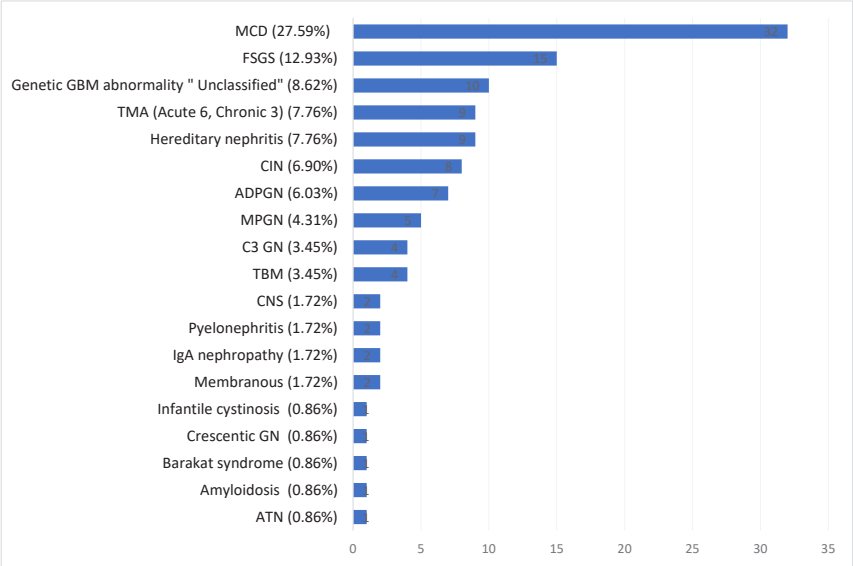

Figure 3. Frequency of renal histopathological diagnoses.

proliferative glomerulonephritis was a known Fabry disease carrier female; EM examination showed zebra bodies within podocytes in association with scattered subepithelial variably sized electron dense deposits (Figure 6). Barakat syndrome patient biopsy (Figure 7), showed a renovascular medial vasculopathy; the interlobular arteries were slightly attenuated with its myocytes as well as those of the arterioles show numerous vacuoles. One of the C3 glomerulopathy cases showed FSGS pattern (Figure 8), and another one with dense deposits had almost normal appearance by light microscopy (Figure 9).

Table 2. Additional histopathological findings in each disease group

Pathological diagnosis	Cortical/Corticomedullary specimen (n)	Global sclerosis (%)	Interstitial fibrosis (%)	Vacuolar degeneration (n)	Arteriolar hyalinosis (n)	Arterial sclerosis (n)
MCD (n= 32)	18/14	1.61 ± 0.03	0	5	2	0
FSGS (n= 15)	7/8	19.81 ± 0.34	26.00 ± 30.38	4	7	2
Genetic GBM abnormality (unclassified) (n= 10)	7/3	0	0	0	0	0
Hereditary nephritis (n= 9)	2/7	0	4.44 ± 13.33	7	2	1
TMA (n= 9):	5/4					
Acute (n= 6)		3.22 ± 0.06	0	0	0	0
Chronic (n= 3)		60.67 ± 30.35	50.00 ± 18.03	0	1	1
CIN (n= 8)	4/4	29.68 ± 13.78	46.25 ± 13.29	0	2	1
ADPGN (n= 7)	2/5	5.29 ± 11.00	6.43 ± 10.69	0	0	0
MPGN (n= 5)	2/3	6.60 ± 13.15	11.60 ± 9.24	0	0	0
TBM (n= 4)	0/4	0	0	0	0	0
C3 GN (n= 4)	1/3	0	8.75 ± 10.31	0	1	0
Membranous (n= 2)	1/1	0	0	1	1	0
IgA nephropathy (n= 2)	1/1	0	0	0	0	0
Pyelonephritis (n= 2)	0/2	17.8 ± 3.18	35.00 ± 49.50	0	0	0
CNS (n= 2)	1/1	22.50 ± 31.80	15.00 ± 21.21	0	0	0
ATN (n= 1)	0/1	0	0	0	0	0
Amyloidosis (n= 1)	0/1	0	5	0	0	0
Barakat syndrome (n= 1)	0/1	0	20	0	0	0
Crescentic GN (n= 1)	0/1	7	5	0	0	0
Infantile cystinosis (n= 1)	0/1	2	20	0	0	0

The values are presented as number (n) and percentage (%).
ADPGN: Acute diffuse proliferative glomerulonephritis, ATN: Acute tubular necrosis, C3GN: C3 glomerulonephritis, CIN: Chronic interstitial nephritis, CNS: Congenital nephrotic syndrome, FSGS: Focal segmental glomerulosclerosis, MCD: Minimal change disease MPGN: Membranoproliferative glomerulonephritis, TBM: Thin basement membrane disease, TMA: Thrombotic microangiopathy.

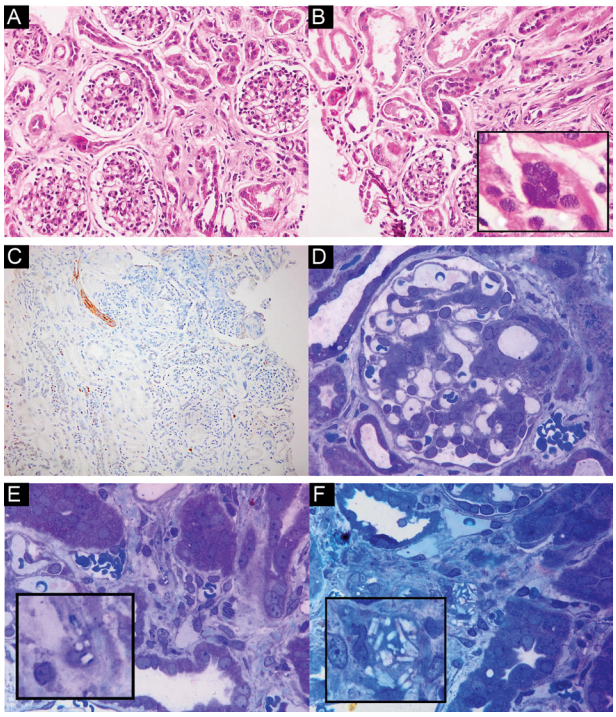

Figure 4. Infantile nephropathic cystinosis (LM and IP). A and B (H and E, ×200): **(A)** The glomeruli show no significant abnormality under LM. **(B)** A proximal tubule shows focal epithelial multinucleation (magnified inside). **(C)** (IP-IgG, ×100): No immune deposits detected. Staining for IgM, IgA and C3 showed no deposits as well. **(D)** (Semi-thin section, toluidine blue, ×400): The tuft shows minimal mesangial hypercellularity. (E and F) (Semi-thin sections, toluidine blue, ×1000): Interstitial mononuclear cells show intracytoplasmic polygonal inclusions of cystine (magnified inside).

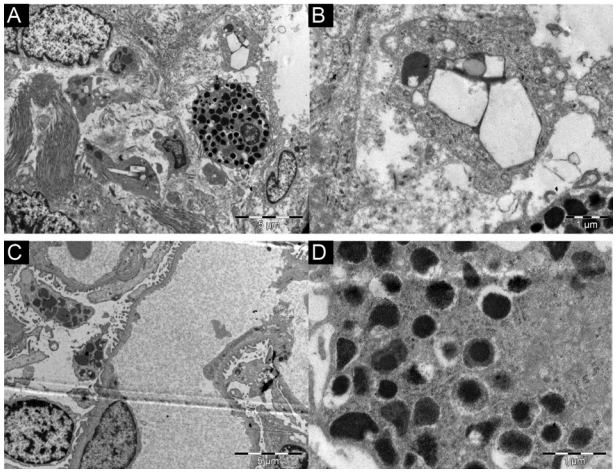

Figure 5. Infantile nephropathic cystinosis (EM). **(A)** (EM, direct magnification ×4000) and **(B)** (EM, direct magnification ×8000): Interstitial cells harboring intracytoplasmic clear hexagonal inclusions as well as dark intensely osmophilic inclusions. **(C)** (EM, direct magnification ×2000): The podocytes show the same inclusions. **(D)** (EM, direct magnification ×24000): Higher magnification of the intralysosomal osmophilic inclusions.

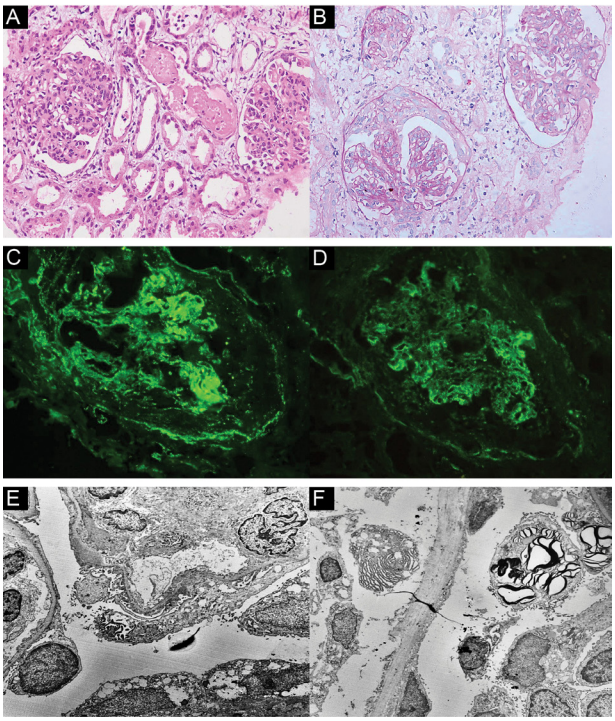

Figure 6. Concomitant ADPGN with Fabry disease carrier status. **(A)** (H and E, ×200): Two glomeruli show global endocapillary hypercellularity with leucocytic influx. **(B)** (PAS, ×200): A cellular crescent is shown in one glomerulus. **(C)** (IF-C3, ×400) and **(D)** (IF-IgM, ×400): The tufts show immune deposits for C3 "score 3+/4+" and IgM "score 2+". **(E)** (EM, direct magnification ×3000): The tufts show scattered electron dense immune deposits. F (EM, direct magnification ×3000): Zebra bodies are detected in visceral epithelial cells.

Discussion

Despite being leading causes of chronic renal damage, the published data about the prevalence and patterns of pediatric renal pathologies are limited, notably those published from the African/Arab countries with lack of published national registries of such diseases from these countries. The aim of this study was to report the prevalence and patterns of these lesions in native kidney needle biopsies in our center from January 2014 to January 2019. The most commonly presenting symptom in our patients was generalized edema followed by hematuria. Similar to the vast majority of pediatric nephropathies reports (3, 5, 9,14-16), nephrotic syndrome was the most common clinical indication for renal biopsy in our patients. Very few other reports had different principle causes like renal manifestations secondary to systemic diseases (4) and non-nephrotic proteinuria (2,7). For primary glomerulonephritis, minimal change disease was the most common pathological diagnosis in our patients (27.59%). A similar observation has been documented in other reports from Africa/Asia by Yuen et al (14%) (4), Yadav et al (58.82%) (6) and Bakr et al (21.77%) (11),

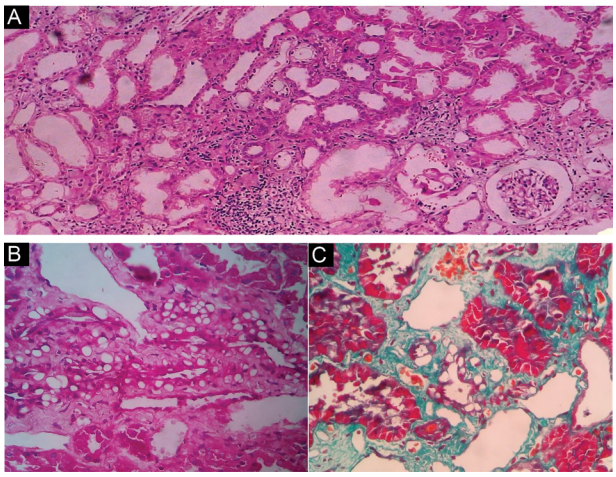

Figure 7. Medial vasculopathy in a case of Barakat syndrome. **(A)** (H and E, ×100): A bird view shows mild interstitial fibrosis associated with mild lymphocytic infiltrate. **(B)** (H and E, ×400) and **(C)** (MT, ×400): The arterioles show numerous myocyte vacuoles reminiscent of those seen with calcineurin nephrotoxicity.

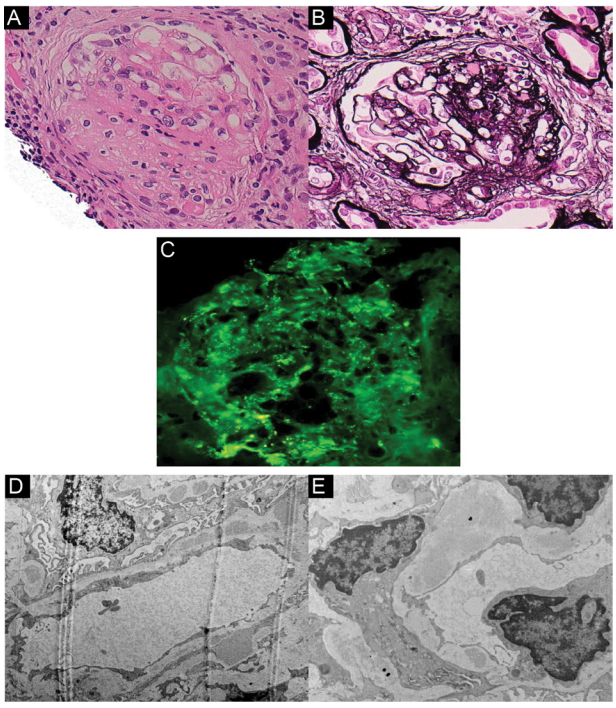

Figure 8. C3 glomerulonephritis (FSGS pattern). **(A)** (H and E, ×400): One glomerulus shows segmental sclerosis with hyaline deposits. **(B)** (JMS, ×400): Another glomerulus shows segmental sclerosis with periglomerular fibrosis. **(C)** (IF-C3, ×400): Intense mesangial and capillary wall deposits of C3 "score 3+/4+" are seen. **(D)** (EM, direct magnification ×6000): and **(E)** (EM, direct magnification ×8000): EM shows mesangial and capillary wall electron dense deposits of C3. The podocytes show segmental effacement of the foot processes.

while IgA nephropathy/Henoch-Schoenlein purpura were dominant in European reports from Italy, Portugal and UK (2, 3, 15), and FSGS in studies from Turkey (7,17) and Serbia (18). In our study, a major proportion of the patients had congenital glomerular diseases (22.41%)

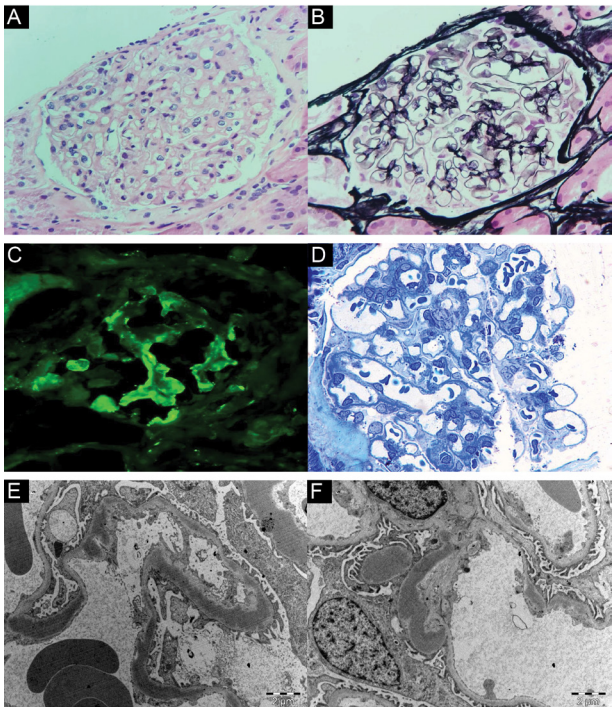

Figure 9. C3 glomerulonephritis (dense deposit disease). **(A)** (H and E, ×400): One glomerulus shows subtle prominence of the capillary wall. **(B)** (JMS, ×400): The same glomerulus; no spikes, capillary wall thickening, or other remarkable changes are seen. **(C)** (IF-C3, ×400): Intense capillary wall deposits of C3 "score 4+" are seen. **(D)** (Semi-thin section, toluidine blue, ×400): Toluidine blue stain is segmentally accentuated in the capillary wall. **(E)** (EM, direct magnification ×10000) and **(F)** (EM, direct magnification ×10000): EM shows Electron dense sausage-shaped deposits in the capillary wall.

that is potentially related to the high incidence of consanguineous marriages in Egyptian population. Unlike similar published works, we gathered under "congenital" umbrella all patients had lesions with a history dating since birth. Ten patients showed features of genetic abnormality of the GBM; not otherwise classified. These cases showed evidence of GBM abnormality by EM that do not fit with any of the well-known patterns of hereditary nephritis. Further classification of these cases was not feasible due to lack of genetic studies in our center. Infantile nephropathic cystinosis is reported as a rare hereditary cause of chronic kidney disease in children in epidemiological registries from America and Europe (1). In our study, one case with infantile nephropathic cystinosis was encountered. This case interestingly showed by EM numerous dark lysosomal inclusions that probably explained by an interpretation proposed by Spear et al (19), as a reaction product of osmium with cystine; however, this histological finding is not previously published online as far as we know. Barakat syndrome is a very rare autosomal dominant disease described by Barakat et al (19), characterized by triad of hypoparathyroidism, sensorineural deafness and renal disease. Very little information available in the

literature about the spectrum of renal histopathological features of this syndrome. Reported lesions include membranoproliferative glomerulonephritis (20), fetal-like glomeruli, renal hypoplasia, dysplasia, cystic changes and nephrocalcinosis (21). The case encountered in our study showed arterial/arteriolar medial vasculopathy pattern reminiscent to calcineurin arteriolopathy. No drug or any other relevant medical history was documented for this patient at the time of presentation. The frequency of other encountered congenital glomerulopathies including Alport type hereditary nephritis (n=9, 7.76%), thin basement membrane disease (n=4, 3.45%) and congenital nephrotic syndrome (n=2, 1.72%) were similar to that reported in other publications (2,9,15). The spectrum of histological patterns of C3 glomerulopathy (dense deposit disease and C3 glomerulonephritis) is wide including mesangial or endocapillary proliferative glomerulonephritis, membranoproliferative GN and crescentic GN (22). Very few cases of C3 glomerulopathy were reported in pediatric renal nephropathy registries from Italy and Saudi Arabia (8,23). In our study, four cases of C3 glomerulopathy (3.45%) were encountered; two of which had unusual histological features for this category; one case of C3 glomerulonephritis showed pure focal segmental glomerulosclerosis without any proliferative lesions. The other case with dense deposits was almost normal by LM; the diagnosis was entirely based on the immunofluorescence and EM findings. This intuitively emphasizes the necessity of ancillary studies to avoid misdiagnosis of such biopsies. Seven of our patients (6.03%) had acute diffuse proliferative glomerulonephritis, mostly post-streptococcal infection. Remarkably, one of which was a known carrier of Fabry disease. The patient EM study showed scattered classic Zebra bodies in association with immune complexes electron dense deposits. The coincidence of both lesions is not reported in the literature as our knowledge reaches. Although IgA nephropathy is the dominant glomerulonephritis in several reports from Europe (2,3,23), a much lower incidence is noticed from Africa/West Asia reports (8,9,11) in keeping with our results. In addition being attributed to sample size and selection criteria; this difference in frequencies reflects a highly possible ethnic and environmental influencers. Hemolytic uremic syndrome stands as cause of ESRD (2-6%) in pediatric renal registries (1). In this report nine patients (7.76%) had thrombotic microangiopathy; six of which presented in acute phase and the rest showed variable features of chronic damage. Only one case of amyloidosis was encountered secondary to familial Mediterranean fever and showed glomerular deposits without other vascular or tubulointerstitial affection. This very low incidence of renal amyloidosis in children is also noticed in other Mediterranean countries' reports (2,7). This study is limited by lack of performing genetic study for the unclassified histological patterns of GBM abnormalities. This report provides information about the prevalence and patterns of pediatric nephropathies in a single center in Egypt that may be useful for epidemiological analysis of such diseases, which is lacking from national registries of the developing countries. Moreover, we present few very rare pediatric renal histopathological findings.

Limitations of the study

The main limitation of this study is lack of performing genetic studies notably for the recorded congenital forms of renal disease.

Authors' contribution

All authors were involved in formatting the study conceptualization, methodology, validation, collecting resources, data curation, formal analysis and writing the original draft of the manuscript. WH and AF conducted manuscript revision and editing.

Conflicts of interest

The authors declare that they have no potential conflicts of interest related to the contents of this article.

Ethical issues

This study followed the tenets of the Declaration of Helsinki. The local ethics committee of our institution approved this study. Accordingly, written informed consent was taken from all participants before any intervention. Besides ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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None.

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