Glomerulonephritis in Children: Experience from the Kuwait Renal Centers

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Key Words

Epidemiology · Glomerulonephritis · Kuwait ·
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Abstract

Objective: To study the clinical, pathological, and epidemiological features of childhood steroid-refractory idiopathic glomerulonephritis (SRIGN), i.e., nephrotic syndrome, which failed an 8-week course of prednisone, and secondary forms of glomerulonephritis (GN) in Kuwait. **Methods:** Data on these two forms of GN were collected retrospectively from the records of children attending the two renal centers of Kuwait between January 1, 1990, and December 31, 1996. **Results:** During the 7 years, a total of 80 children were diagnosed to have GN, 56 of whom were Kuwaiti nationals. In the latter group, 34 children had SRIGN. Hence, the calculated annual incidence rate of Kuwaiti children with both GNs was 3.1 per million and that for SRIGN was 1.9 per million children. Histologically, 22 (65%)

of these patients had minimal change, 5 (16%) focal segmental, 2 (6%) non-IgA mesangio-proliferative, and 1 membranous GN. Congenital nephrotic syndrome, membranoproliferative GN, and GN secondary to parasitic infestations or microbial infections were not seen in the Kuwaiti children, and nephrotic syndrome secondary to IgA glomerulopathy was diagnosed in 1 patient only. Aggressive autoimmune diseases such as systemic lupus erythematosus (SLE) and vasculitis were common. Seven patients had SLE which accounted for 44% of secondary GN and for 14% of all the patients included in the study, while 3 patients were found to have vasculitis. Interestingly, only 3 of the 13 patients with SLE and vasculitis presented with rapidly progressive GN. **Conclusions:** The pattern of renal disease associated with SRIGN in Kuwaiti children is different from that reported from neighboring countries and other Arab states. The homogeneity of the population studied, lack of endemic infections or parasitic infestations, and genetic predisposition may have

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been the underlying factors. Furthermore, the high incidence of the insidious kidney-limited disease associated with SLE and vasculitis is another feature which indicates a more aggressive diagnostic approach in the management of GN in our area.

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Introduction

Contrary to adults, data on the clinical, pathological, and epidemiological features of glomerulonephritis (GN) in children are limited. Multiple factors have contributed negatively to such a phenomenon, of which the slow emerging status of pediatric nephrology as an independent subspecialty, as compared with the adult one, and the limitations akin to kidney biopsy in children are of paramount importance. The latter, though, was seriously affected by the former, remained a major handicap in the assessment and management of these sick children. The high proportion (>85%) of children with steroid-responsive 'idiopathic' nephrotic syndrome (NS) and the need for an experienced operator, radiological assistance, and general anesthesia in younger children were cogent arguments in favor of limiting such an invasive procedure to those who manifest steroid refractoriness [1] or signs of secondary GN. Data on these forms of GN are slowly emerging from different societies [2], though most have been affected by the limited number of cases studied, referral bias of tertiary centers, difference in biopsy indications, admixture of different populations, and limited area of coverage [3–6]. The present study was conducted to examine the clinical, pathological, and epidemiological features of these forms of GN in the Kuwaiti children and compare these to those previously reported from Kuwait and other parts of the world.

Patients and Methods

Kuwait is an Asian country located on the north-eastern part of the Arabian peninsula and has an area of 17,818 km² (6,960 square miles). In mid-1993, it had a population of 1.4 million, of which 0.62 million (43%) were Kuwaiti nationals. In the latter group, 254,976 were ≤ 14 years old. In these Kuwaiti children, the male:female ratio was 1:1.

Study Design

Data on children referred for the management of GN, excluding kidney transplant patients, who were seen at the Al-Amiri and the Mubarak Al-Kabeer hospitals were collected retrospectively in December 1996. These hospitals are the two teaching hospitals of the Kuwait University, and their renal centers are the only facilities specialized for the care of both adult and childhood renal diseases. The study period covered 7 years, from January 1, 1990, to December 31, 1996. Children were included in the study if they had: (1) steroid-refractory idiopathic GN (SRIGN), i.e., those who failed the 8-week course of prednisone therapy (see below) or (2) a secondary form of GN.

Clinical and Laboratory Data

The data collected included: age of the patient at diagnosis of GN, sex and nationality, as well as the clinical manifestations of GN and its duration and response to corticosteroid therapy. Laboratory investigations included urinalysis, 24-hour urinary protein excretion, and creatinine clearance as well as serum cholesterol, complements (C3 and C4), immunoglobulins, antinuclear antibody, anti-dsDNA, antineutrophil cytoplasmic autoantibody, hepatitis B surface antigen, hepatitis C virus antibodies, ASOT, and rheumatoid factor. Histological diagnosis of GN was made based on the results of: (1) light microscopic examination of 2-μm sections of renal tissues which were stained with hematoxylin and eosin, periodic acid-Schiff, Masson's trichrome, and periodic acid-silver methenamine; (2) immunofluorescence using antisera against C3, fibrinogen, and immunoglobulins (IgA, IgM and IgG), and (3) electron microscopy in selected patients.

Indications for Kidney Biopsy

Over the past 7 years, all patients who were referred to the two renal centers were considered for kidney biopsy, if they manifested one of the following criteria: (1) NS (persistent proteinuria >40 mg/h/m²) which failed to respond to an 8-week course of prednisone (2 mg/kg every 2nd day); (2) persistent proteinuria of any degree (>4 mg/h/m²) with unexplained hematuria;

Table 1. Clinical features of children with GN in Kuwait (1990–1996)

Diagnosis	Number of patients	Male/female ratio		Signs of renal disease			Clinical presentation at diagnosis			
		Kuwaiti	non-Kuwaiti	hyper-tension	protein-uria	hema-turia	NS	rapidly progr. renal failure	chronic renal failure	multi-system disease
<i>Idiopathic nephrotic syndrome</i>										
Minimal-change disease	33	13/9	7/4	2	33	1	33	0	0	0
Focal segmental glomerulosclerosis	6	3/2	0/1	4	6	4	5	1	0	0
Mesangioproliferative (non-IgA) glomerulosclerosis	5	1/1	1/2	3	5	3	4	0	0	0
Congenital nephrotic syndrome	2	0/0	1/1	0	2	0	2	0	0	0
Membranous GN	1	1/0	0/0	0	1	0	1	0	0	0
<i>Secondary GN</i>										
SLE	8	2/5	0/1	7	8	8	2	2	1	3
Vasculitis	5	1/2	0/2	4	3	5	1	1	1	2
Poststreptococcal GN	4	1/1	1/1	4	4	4	4	0	0	0
Immunoglobulin A glomerulopathy	2	1/0	1/0	2	2	2	1	1	0	0
Henoch-Schönlein purpura	2	1/1	0/0	2	2	2	2	0	0	0
Alport's disease	1	1/0	0/0	1	1	1	0	0	1	0
<i>Unclassified</i>										
Sclerosing GN	2	1/1	0/0	2	2	1	2	0	0	0
Biopsy refused	4	3/1	0/0	0	4	0	4	0	0	0
Bilateral small kidneys (unbiopsied, yet GN suspected)	5	3/1	1/0	3	5	5	2	0	1	0
Total	80	32/24	12/12	34	75	33	63	5	6	5

(3) isolated hematuria unexplained by hematological, renovascular, or urinary tract disease; (4) rapidly progressive renal failure (i.e., rapid decline in creatinine clearance over 3–6 weeks), and (5) unexplained renal failure with normal-sized kidneys.

Results

Epidemiological Profile

During the study period, a total of 80 children were diagnosed as having SRIGN or secondary GN, 56 of whom were Kuwaiti nationals (table 1). Forty-seven patients had histological and clinical evidence of SRIGN, 30 of whom were Kuwaiti nationals, and 22 had secondary forms of GN. Eleven patients had evidence of glomerulopathy, but were histologically unclassified. This group consisted of

2 patients with advanced sclerosing GN, 4 who refused kidney biopsy, and 5 who presented with bilateral small kidneys and yet had a history of NS. The 4 patients who refused kidney biopsy did not have systemic manifestations of autoimmune disease, extrarenal systemic involvement, renal failure, or abnormal urinalysis. For analysis purposes, and based on these clinical criteria as well as their presentation as a frequently relapsing NS, the latter 4 patients were included in the study as having idiopathic NS. Hence, the calculated average annual incidence rate of Kuwaiti children with SRIGN and secondary GN was 3.1 per million and that of SRINS alone was 1.9 per million for Kuwaiti children. In Kuwaiti nationals, males were 1.3 times the females. When the distribution of patients, according to their diagnosis, was

Fig. 1. Scatter diagram showing the age distribution of children with GN according to the histological type. ● = Idiopathic nephrotic syndrome; □ = secondary forms of GN. MCD = Minimal-change disease; FSGS = focal segmental glomerulosclerosis; MGN = membranoproliferative GN; HSP = Henoch-Schönlein purpura.

plotted against their respective age at the time of diagnosis, none of the patients with secondary forms of GN, except for 1 patient with Alport's syndrome, presented before the age of 60 months (fig. 1).

Etiology of GN

The underlying renal disease in all patients is shown in table 1. In the Kuwaiti nationals, 34 patients (61%) were classified as having SRIGN, 30 of whom underwent renal biopsy. Histologically, 22 (65%) of these patients were classified as having minimal-change NS, 5 (16%) as having focal segmental glomerulosclerosis, 2 (6%) as having non-IgA mesangioproliferative GN, and 1 as having membranous GN. After the exclusion of 1 patient with

Alport's syndrome, 14 of the 15 patients studied presented with NS with or without renal failure. Aggressive autoimmune diseases such as systemic lupus erythematosus (SLE) and vasculitis were common. Seven patients had SLE which accounted for 44% of secondary GN and for 14% of all patients studied, while 3 patients were found to have vasculitis. In general, congenital NS and membranoproliferative GN were not seen in the Kuwaiti children, and NS secondary to IgA glomerulopathy was diagnosed in 1 patient only. During our study, parasitic infestations or microbial infections such as malaria, leishmaniasis, schistosomiasis, tuberculosis, brucellosis, hepatitis B or C, and congenital syphilis were not seen in our Kuwaiti patients.

Clinicopathological Correlations

The spectrum of renal disease associated with SRIGN and secondary forms of GN is summarized in table 1. NS was the presenting feature of all patients with SRIGN, except for 1 patient with focal segmental glomerulosclerosis who presented with persistent proteinuria (32 mg/h/m²), hematuria, and rapidly progressive renal failure. Hypertension and hematuria were rarely encountered in patients with minimal-change disease, in contrast to patients with focal segmental glomerulosclerosis and mesangioproliferative GN (67 and 60%, respectively). On the other hand, 10 of the 22 patients with secondary forms of GN presented with NS, and most had hypertension and hematuria. Interestingly, only 3 of the 13 patients with SLE and vasculitis presented rapidly progressive renal failure and 5 with multisystem disease.

Discussion

In the present study, a total of 56 Kuwaiti children were diagnosed to have either SRIGN or secondary forms of GN over the past 7 years. The study was not designed to be representative of all GN in Kuwaiti children for two reasons: (1) as in any similar studies conducted in tertiary units, patients with mild forms of GN may escape inclusion due to underdiagnosis or failure to report, and (2) children in whom the diagnosis of NS has been made, clinically as idiopathic, based on the absence of risk factors (hypertension, hematuria, raised serum creatinine, low plasma C3) and manifested cure of infrequent relapses after corticosteroid therapy by their primary pediatrician may be difficult to follow in any retrospective study [1, 7]. For these reasons, the study concentrated on children with SRIGN and those with severe forms of secondary GN, in whom alternatives to the

conventional 8-week corticosteroid therapy are to be used and the risk of complications of the disease or side effects of therapy requires specialized care. Moreover, the management of the latter group of patients, due to their high rate of short- and long-term morbidity [8], is a major health concern, both financially and socially. Our study has covered the whole country of Kuwait and excluded the 'unstable' expatriate population. Moreover, the liberal policy of the referral to the specialized centers and the free-of-cost management to all social strata have helped to generate our results which should reflect the true pattern of the epidemiological characteristics of refractory GN in Kuwaiti children. Our observation of an annual incidence rate of 1.9 Kuwaiti children with SRIGN per 100,000 is nearly double that reported from an earlier study from Kuwait [3]. Our study is more likely to be representative of the true incidence of SRIGN in Kuwait, since the previous study was conducted in a general hospital on the outskirts of Kuwait and covered two undefined population areas. Furthermore, in the former study, children from other Arab states were included in the analysis. Such a methodology may have been responsible for the difference in the histological diagnosis of their 9 patients with SRIGN as compared with our study. In the former study, 5 out of 9 children with SRIGN had membranoproliferative GN, while this GN was not seen in any Kuwaiti children over 7 years of observation. This form of GN has been reported with relatively higher frequency in Arab patients from the Mediterranean countries [9] and in those with infections such as hepatitis (B and C) [10, 11], malaria [12], and schistosomiasis [13, 14]. In the Iranian experience [5], membranoproliferative GN was diagnosed in 80 of their 411 patients (19%) with GN as compared with 2 in the 25 patients (8%) in the Saudi children [4]. In our study, minimal-change GN was the most

frequent histological diagnosis in patients with SRIGN in general, while focal segmental glomerulosclerosis was the predominant lesion in those who manifested steroid resistance. These features may have been different from those reported in the Irani and Saudi studies [4, 5], yet are similar to those described by Churg et al. [15] and McEnery et al. [16] in a North American population.

The spectrum of secondary GN in Kuwaiti children is interesting. Though the incidence of certain GN such as postinfectious and benign hematuria syndromes may have been underestimated for methodological reasons, that of others such as lupus nephritis and renal vasculitis was not. The latter two GN were not rare and accounted for 17% of the

total GN referred for management. Though these entities were reported as uncommon GN in Western countries [15, 16], SLE was seen in 33 of the 411 patients (8%) subjected to kidney biopsy in Iran and vasculitis in 9 (2%) [5]. The relatively higher incidence of these two forms of GN may have been a reflection of ethnic predisposition, yet the higher incidence of patients with kidney-limited lupus and vasculitis as well as the presentation of NS in 3 patients are disturbing findings. The latter two findings may have been the result of a better surveillance in our study population, yet they provide a cogent argument in favor of adopting an aggressive diagnostic approach in the management of childhood GN.

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