Study of patients with nephrotic syndrome in Sohag University Hospital

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Background
Nephrotic syndrome is not a disease; it is the manifestation of a wide variety of underlying disease processes.

Objectives
The aim of the present study was to investigate different clinic-laboratory and histological patterns of nephrotic syndrome and the relationship between its clinical character and prognosis.

Methods
From January 2010 to December 2011 the authors of the present study retrospectively and prospectively studied 139 patients with nephrotic syndrome, diagnosed on the basis of heavy proteinuria greater than 3 g/day, hypoalbuminemia, evidence of fluid retention or edema, and hyperlipidemia.

Results
A total of 139 patients (M : F = 79 : 60) were included in the present study; their mean age was 33.9 ± 13.47 years (primary : secondary nephrotic syndrome = 80 : 59). Systemic lupus erythematosus was the most common underlying cause of secondary nephrotic syndrome [24 cases (40.7%)], followed by DM [13 cases (23.7%)]. Renal biopsy revealed 18 patients (30.5%) with membranoproliferative glomerulonephritis, 15 (25.43%) with membranous nephropathy, seven (11.86%) with mesangial proliferative glomerulonephritis, six (10.16%) with amyloidosis, five (8.47%) with focal segmental glomerulosclerosis, three (5.08%) with diffuse proliferative glomerulonephritis, one (1.69%) with focal proliferative, minimal mesangial, sclerosing glomerulonephritides, one patient (1.69%) with crescent glomerulonephritis, and another one (1.69%) with IgA nephropathy. A raised serum creatinine level was found in 49 (35%) patients, and 35 (74.4%) of them had normal renal function at the last follow-up. Complete remission of proteinuria occurred in 69 (49.6%) patients, partial remission in 53 (38.1%), and resistant proteinuria in 17 (12.2%).

Conclusion
Clinical features and biochemical values do not give many clues about the underlying histological types of glomerulonephritis. Therefore, renal biopsy should be carried out in all patients with adult nephrotic syndrome, as results permit us to establish a specific diagnosis, which helps in counseling the patients about the likely prognosis of their disease and to select a specific therapeutic regimen.

Keywords:
clinical pattern, membranoproliferative glomerulonephritis, prognosis, renal biopsy

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Introduction

The traditional terminology and classification of the nephrotic syndrome (NS) dates back to Muller [1], who first described in 1905 the separation of the term 'nephrosis' from nephritic diseases. Since these early studies, clinicians have come to realize that like fever, NS is not a disease; it is the manifestation of a wide variety of underlying disease processes. The NSs are a common constellation of abnormalities that include proteinuria, edema, hyperlipidemia, hypoalbuminemia, and hypercoagulability. It can be caused by underlying systemic diseases or direct injury to the kidney [2].

NS may affect adults and children, of both sexes and of any race. It may occur in a typical form, or in association with nephritic syndrome. The latter consists of glomerular inflammation, with hematuria and impaired kidney function [3]. Making an accurate diagnosis of underlying glomerulonephritis (GN) requires a combination approach including clinical data, serologic tests, and complete pathologic evaluation of renal biopsy by using light microscopy and immunoflourescence [4–8].

Results of many studies indicate that focal segmental glomerulosclerosis (FSGS) is the single most common

cause of NS in adults, followed by minimal change NS and IgA nephropathy [9]. Prognosis varies according to the cause. Complete remissions may occur spontaneously or with treatment. The prognosis generally is favorable in corticosteroid-responsive disorders.

Recurrence rate is high in patients who have underwent kidney transplantation, with FSGS, systemic lupus erythematosus (SLE), IgA nephropathy, amyloidosis, and membranoproliferative GN (especially type II) [10].

To our knowledge, there is no study on the local population where light microscopy and serological assessment has been carried out in patients with NS, its clinical presentations, steroid responsiveness, subsequent clinical course, and patterns of relapse.

Objectives

Large numbers of patients with NS in Sohag University Hospital were put under close observation to:

(1) Evaluate different clinical patterns of NS.
(2) Determine the correlation between the clinical patterns and etiology of NS.
(3) Determine the relationship between the clinical character, therapeutic response, and the prognosis of NS.

Patients and methods

The study was carried out at the internal medicine department at Sohag University Hospital, over a period of 2 years (2010–2011). The study was approved by the Scientific and Ethical committees at Sohag Faculty of Medicine. An informed consent was obtained from all participants.

This was an observational, nonrandomized clinical and laboratory study involving retrieval of clinical and laboratory data from a review of original records of patient's follow-up, and of newly diagnosed patients, by investigating patients with NS, its clinical presentations, subsequent clinical course, and patterns of relapse. A total of 139 patients (age more than 12 years) with NS, diagnosed on the basis of massive proteinuria greater than 3 g/day, hypoalbuminemia, evidence of fluid retention or edema, and hyperlipidemia, were included in this study. All the cases were studied after meticulously taken history and clinical findings. All patients were investigated for the possible causes of secondary NS, like fasting blood sugar, 2 h postprandial, HBsAg, anti-HCV, and patient with suspected SLE were investigated for antinuclear factor, anti-dsDNA and C3, C4. All the patients were evaluated for urine, blood urea, serum creatinine, 24 h urinary total proteins, serum cholesterol, serum total protein, and serum albumin; ultrasonography of the genitourinary system was carried out; in addition, renal biopsy was carried out in indicated cases, especially in older participants. Renal biopsy was carried out for 59 patients with 'needle biopsy' with all the aseptic precautions. A bone marrow aspiration and malignancy screening were carried out for selected patients with suspected myeloma and amyloidosis.

Treatment

A total of 80 patients were diagnosed with primary NS; 77 of them were treated with corticosteroid or immunosuppressive agents and three patients showed spontaneous recovery. Patients who did not respond to corticosteroids were treated with immunosuppressive agents. In total, 23 patients were treated with steroid and azathioprin; nine patients with steroid, azathioprin, and cyclophosphamid; seven patients were treated with steroid and cyclophosphamid; and one patient was treated with steroid and cyclosporine. Patients with SLE were treated with corticosteroid and immunosuppressive agents; diabetic and hypertensive patients were treated with ACE inhibitors. Patients with amyloidosis were treated with ACE inhibitors and Colchicines. Others were treated according to the cause of the disease. The mean duration of follow-up was 14.22 ± 11.17 months.

Statistical analysis

Descriptive statistics were calculated for quantitative variables (mean, SD, minimum and maximum) and for qualitative ones (absolute and percent frequencies). Mean of quantitative variables were compared by using Student's *t*-test and those of qualitative ones were compared by using the χ^2-test. We used SPSS statistical software, version 17 (SPSS Inc., Chicago, Illinois, USA), and results were considered significant when *P*-value was less than 0.05, and highly significant when it was less than 0.001.

Results

A total of 139 patients who fulfiled the inclusion criteria were followed-up for 14.22 ± 11.17 months. The study included 79 (56.8%) men and 60 (43.2%) women. Their age range was 13–68 years; the common age group was 12–29 years (53.2%). The main demographic characteristics are shown in Table 1.

In total, 62 (44.6%) patients presented with puffiness with lower limb edema; 20 (14.4%) with lower limb

Table 1 Demographic characteristics of patients

Parameters	Age				Total	*P*-value
	12–29	30–44	45–60	>60		
N (%)	74 (53.2)	30 (21.6)	21 (15.1)	14 (10.1)	139 (100)	–
Male/female	38/36	15/15	15/6	11/3	79/60	–
Rural/urban	60/14	24/6	18/3	11/3	113/26	–
Smoking [*n* (%)]	3 (10)	6 (20)	14 (46.7)	7 (23.3)	30 (100)	–
Serum albumin (mg/dl)	1.9 ± 0.59	1.99 ± 0.83	1.97 ± 0.61	2 ± 0.68	1.94 ± 0.66	0.9
Serum cholesterol (mg/dl)	358.5 ± 114.5	340.1 ± 130.9	268 ± 49.2	258 ± 103.08	330.7 ± 120.0	0.001
Serum triglyceride (mg/dl)	279.4 ± 105.1	288.7 ± 131.3	221.4 ± 73.3	212.1 ± 94.2	265.9 ± 109	0.023
Serum creatinine (mg/dl)	1.62 ± 1.85	1.64 ± 1.32	3.57 ± 3.18	4.24 ± 4.05	2.18 ± 2.48	<0.001
24 h urinary total proteins (g/24)	7.05 ± 5.1	8.08 ± 5.53	5.6 ± 4.08	4.6 ± 2.25	6.8 ± 4.9	0.14
Significant azotemia	17/74	11/30	12/21	9/14	49 (35.5)/139	0.002

edema, puffiness, and frothy urine; 15 (10.8) with lower limb edema, puffiness, and ascitis; 10 (7.2%) with lower limb edema; and 23 (16.4%) with lower limb edema, puffiness, frothy urine, ascitis, and pleural effusion. Patients were classified according to the etiology: 80 (57.5%) cases had primary or idiopathic NS and the remaining 59 (42.5%) had NS due to some other diseases (secondary NS), as is shown in Table 2.

Table 2 Etiological classification of nephrotic syndrome

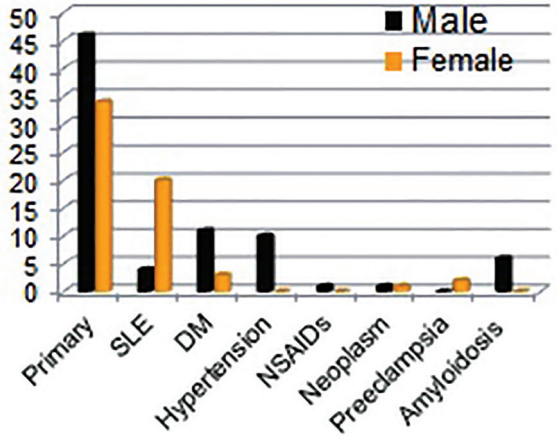
Classification	Frequency (%)
Primary	80 (57.55)
SLE	24 (17.26)
DM	14 (10.07)
Hypertension	10 (7.15)
Amyloidosis	6 (4.31)
Neoplasm (myeloma)	2 (1.43)
Pre-eclampsia	2 (1.44)
NSAIDs	1 (0.71)
Total	139 (100)

DM, diabetes mellitus; SLE, systemic lupus erythematosus.

Etiological classification of nephrotic syndrome

Primary NS was the most common clinical pattern in all the age groups shown, but the incidence of SLE and amyloidosis decreased with age and that of diabetes mellitus (DM) increased with age. Primary NS, SLE, and amyloidosis were common in patients in the age group 12–29 years and hypertension in the age group 45–60 years, but DM was more common in the age group greater than 60 years. Primary NS, amyloidosis, NS secondary to hypertension, and DM were common in male participants, but SLE was common in female participants (Fig. 1). Amyloidosis (10 550 ± 7369.3 mg/24 h) is the most common cause of heavy proteinuria, followed by primary NS (7594.6 ± 5573.5 mg/24 h). In total, 52 (37.4%) patients presented with microscopic hematuria, which was found in NS secondary to NSAIDs, myeloma, SLE, and primary NS.

Figure 1



Etiological classification of nephrotic syndrome. DM, diabetes mellitus; SLE, systemic lupus erythematosus.

Complications

Infection in 119 patients (85.6%) was found in amyloidosis, neoplasm, then SLE, and DM, such as bacterial infections, especially pneumonia, abscess, gastroenteritis and sepsis (P = 0.017). Significant azotemia in 49 patients (35.2%) was found in NS secondary to neoplasm, hypertension, NSAIDs, and then amyloidosis (P = 0.001). Hypertension was detected during follow-up in 34 patients (24.4%) in pre-eclampsia, DM, amyloidosis, and then in SLE (P = 0.13), as shown in Table 3.

Hematuria in 13 patients (9.3%) was found in NS secondary to NSAIDs, neoplasm, hypertension, primary NS, and SLE (P = 0.04). Newly diagnosed DM occurred in 11 patients (7.9%) as a treatment complication. Six of them were SLE and five were primary NS (P = 0.114). Thrombosis as a complication of NS occurred in eight (5.7%) patients in the first 6 months of diagnosis, which was similar in SLE in two (8.3%) out of 24 patients, primary NS in four (5%) out of 80 patients, DM in one (7%) out of 13 patients, and neoplasm in one (50%) out of two patients ($P \leq 0.001$). Deep venous thrombosis (DVT)

Table 3 Complications found in the study group

Classification	Infection	Hypertension	Significant azotemia	Hematuria	Total
Primary	68	19	23	8	80
SLE	23	6	3	2	24
DM	10	5	9	0	14
Hypertension	9	0	7	1	10
NSAIDs	1	0	1	1	1
Neoplasm	2	0	2	1	2
Pre-eclampsia	2	2	0	0	2
Amyloidosis	6	4	2	0	6
Total [*n* (%)]	119 (85.6)	34 (24.4)	49 (35.2)	13 (9.3)	139

DM, diabetes mellitus; SLE, systemic lupus erythematosus.

occurred in three (2.1%) patients, and was the most common type of thrombosis; two patients had cerebral infarction, and there was only one case of pulmonary embolism. DVT with pulmonary embolism and myocardial infarction with acute limb ischemia were detected. The relative risk of pulmonary embolism was 1.4% and was especially high in the age group 30–44 years. Arterial thrombosis was (0.7% of the patients) less common than was venous thrombosis (2.1% of the patients).

Histological classification of nephrotic syndrome

Renal biopsy was carried out for 59 patients with NS to evaluate the histopathological pattern. Membranoproliferative GN was the most common underlying cause, which was found in 18 (30.5%) cases; membranous nephropathy was found in 15 (25.43%) cases, mesangial proliferative GN in seven (11.86%), amyloidosis in six (10.16%), FSGS in five (8.47%), diffuse proliferative GN in three (5.08%), focal proliferative, minimal mesangial, sclerosing glomerulonephritides in one patient (1.69%), crescent GN in one patient (1.69%), and IgA nephropathy in another case (1.69%), as shown in Table 4.

Membranous nephropathy was the most common histological pattern in all the age groups shown, but the incidence of membranoproliferative GN, amyloidosis, and FSGS were common in young age. Mesangial proliferative, FSGS, amyloidosis, diffuse proliferative, and minimal mesangial GN were common in men, but membranoproliferative GN, membranous nephropathy, and IgA nephropathy were common in women. Amyloidosis was the most common cause of heavy proteinuria, followed by mesangial proliferative, focal proliferative, membranoproliferative GN, and membranous nephropathy.

Complications

Infection in 52 patients (96.6%) was the most common complication, which was found in amyloidosis, followed by membranous nephropathy, mesangial proliferative, focal proliferative, membranoproliferative GN, and FSGS (Table 5).

Table 4 Histological types found in the study group

Biopsy	Total [*n* (%)]	Sex [*n* (%)]	
		Male	Female
Membranoproliferative glomerulonephritis	18 (30.50)	8 (44.4)	10 (55.6)
Membranous nephropathy	15 (25.43)	7 (46.7)	8 (53.3)
Mesangial proliferative	7 (11.68)	4 (57.1)	3 (42.9)
Amyloidosis	6 (10.16)	6 (100)	0
Focal segmental glomerulosclerosis	5 (8.40)	4 (80)	1 (20)
Diffuse proliferative	3 (5.08)	2 (66.7)	1 (33.3)
Minimal mesangial	1 (1.69)	1 (100)	0
Focal proliferative	1 (1.69)	0	1 (100)
Crescent glomerulonephritis	1 (1.69)	0	1 (100)
Sclerosing glomerulonephritides	1 (1.69)	1 (100)	0
IgA nephropathy	1 (1.69)	0	1 (100)
Total	59 (100)	33 (55.9)	26 (44.1)

Hypertension in 16 patients (27.1%) as a complication, detected during the follow-up, was found in FSGS, diffuse proliferative, crescent GN, and amyloidosis. Azotemia in 26 patients (44%) was found in FSGS, amyloidosis, focal proliferative GN, and membranous nephropathy.

Hematuria in five patients (8.5%) was found in IgA nephropathy, diffuse proliferative, and mesangial proliferative GN. Thrombosis in four patients (6.8%) as a complication was found in membranoproliferative and minimal mesangial GN (*P*-value was significant). The most common types of thromboses were DVT, cerebral infarction, and pulmonary embolism. The risk of thrombosis was 16% in membranoproliferative GN. One patient had a myocardial infarction in membranoproliferative GN, and only one patient had minimal mesangial-developed pulmonary embolism. DM in four patients (6.8%) as a complication, detected during the follow-up with treatments, was found in membranoproliferative GN, focal proliferative GN, and mesangial proliferative GN.

Table 5 Relation between complications and histological pattern

Histological pattern	*n* (%)				
	Infection	Hypertension	Significant azotemia	Hematuria	Total
FSGS	4 (80)	3 (60)	3 (60)	0	5
FPGN	—	1	1	0	1
DPGN	3 (100)	1 (33.3)	1 (33.3)	1 (33.3)	3
MN	14 (93.3)	3 (20)	6 (40)		15
MPGN	15 (83.3)	3 (16.7)	6 (33.3)	2 (11.1)	18
SGN	1	—	1	0	1
MesGN	1	1	0	0	1
MesPGN	7 (100)	1 (14.2)	2 (28.5)	1 (14.2)	7
CGN	1	1	1	0	1
Amyloidosis	6 (100)	2 (33.3)	4 (66.6)	0	6
IgA N	0	0	1	1	1
Total	52 (96.6)	16 (27.1)	26 (44)	5 (8.5)	59

FSGS = focal segmental glomerulosclerosis, FPGN = focal proliferative glomerulonephritis, DPGN = diffused proliferative glomerulonephritis, MN = membranous nephropathy, MPGN = membrano-proliferative GN, SGN = sclerosing glomerulonephritides, MesGN = minimal mesangial, MesPGN = mesangial proliferative, CGN = crescent GN.

Hypertension with renal failure and anemia are features of more serious renal disease (e.g. FSGS, amyloidosis, mesangial proliferative GN, and crescentic nephritis) rather than other histological types.

Treatment

Primary nephrotic syndrome

Steroids: In 80 patients with the primary NS, three (3.2%) patients showed spontaneous recovery. On the basis of the therapeutic response of 77 patients to steroids, 12 (15.6%) patients had complete remission, eight (10.4%) patients had partial remission, seven (9.1%) patients had infrequent relapse, eight (10.4%) patients had frequent relapse, 10 (12.9) patients were steroid-dependent, and 32 (41.6%) patients were steroid-resistant, as shown in Fig. 2.

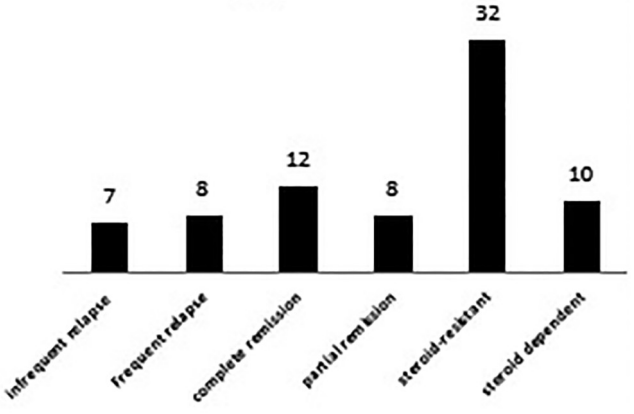
The incidence and the number of relapse (one up to seven relapses) increased in younger patients, age from (12–29 years) 23 (46%) cases and decrease by age (P = 0.017) as shown in Table 6.

Renal biopsy was carried out for 49 cases with primary NS, and according to steroid therapy response, complete remission occurred in one (14%) patient with mesangial proliferative GN; partial remission occurred in two (40%) patients with FSGS, three (21%) patients with membranous nephropathy, two (11%) patients with membranoproliferative GN, and one patient (14%) with mesangial proliferative GN; frequent relapsing occurred in one (20%) patient with FSGS, two (14%) with membranous nephropathy, one (14%) with mesangial proliferative GN, and one (5.8%) with membranoproliferative GN. Steroid-dependency was detected in three (17.6%) patients with membranoproliferative GN, and in only patient with diffuse proliferative GN. Steroid resistance was seen in nine (64%) patients with membranous nephropathy,

Table 6 Relation between steroid therapy response and age group of primary nephrotic syndrome

Steroid response	Age group [*n* (%)]				Total
	12–29	30–44	45–60	>60	
Infrequent relapse	7 (14)	—	—	—	7
Frequent relapse	5 (10)	1 (4.5)	1 (16.7)	1 (50)	8
Complete remission	10 (20)	2 (9)	—	—	12
Partial remission	4 (8)	3 (13.6)	1 (16.7)	—	8
Steroid-resistant	16 (32)	11 (50)	4 (66.7)	1 (50)	32
Steroid-dependent	7 (14)	3 (13.6)	—	—	10
Not used	1 (2)	2 (9)	—	—	3
Total	50 (100)	22 (100)	6 (100)	2 (100)	80

Figure 2



Steroid therapy response in primary NS. NS, nephrotic syndrome.

four patients (57%) with mesangial proliferative GN, nine (52%) with membranoproliferative GN, two (40%) patients with FSGS, and one patient each with focal proliferative GN, sclerosing GN, and mesangial GN. Spontaneous recovery occurred in two (11.70%) patients with membranoproliferative GN (P < 0.001).

Combination therapy response: Combination therapy was used in 44 patients. Complete remission occurred

in 26 (59%) patients and was more common in the age group 45–60 years; partial remission occurred in 16 (36.6%) patients and was more common in the age group 30–44 years; steriod resistance was detected in two (4.5%) patients and was more common in the age group 30–44 years.

Types of combination therapy

A total of 27 patients were treated with steroid and azathioprin. Complete remission occurred in 13 (48.1%) patients, partial remission in 13 (48.1%), and steroid resistance was seen in one (3.7%).

Nine patients were treated with steroid, azathioprin, and cyclophosphamid. Complete remission occurred in five (55.5%) patients, partial remission occurred in three (33.3%), and steroid resistance was seen in one patient (11.1%).

Seven patients were treated with steroid and cyclophosphamid; complete remission occurred in five (71.4) patients and partial remission occurred in two (28.5%).

One patient was treated with steroid and cyclosporine, who showed complete remission, as shown in Table 7.

SLE

In 24 patients with SLE, on the basis of their therapeutic response to steroids, four (16.6%) patients went into partial remission, three (12.5%) patients went into infrequent relapse, one (4.1%) patient was found to be steroid-dependent, and 16 (66.6%) patients were found to be steroid-resistant.

Combination therapy response

A total of 16 patients were treated with steroid, azathioprin, and cyclophosphamid: complete remission occurred in eight (50%) patients, partial remission occurred in six (37.5%) patients, and steroid resistance was detected in two (12.5%) patients. Six patients were treated with steroid and cyclophosphamid: complete remission occurred in three (50%) patients, partial remission occurred in two (33.3%) patients, steroid resistance was seen in one patient (16.7%). Complete remission occurred in only patient who was treated with steroid and azathioprin.

Prognosis

Renal function

A total of 49 (35%) patients presented with renal insufficiency at the start of the study; 23 (46.9%) of them had primary NS and 26 (53%) had secondary NS.

After 6 months of treatment, 30 (61.2%) patients had normal renal function and five (10.2%) received dialysis, and then it was stopped; 14 (28.5%) patients were on dialysis until the end of the study, as shown in Table 8.

The most common causes of end-stage renal diseases in secondary NS were amyloidosis [2/6 (33.3%) patients], hypertension [3/10 (30%) patients], DM [1/13 (7.7%) patients], neoplasm (myeloma) (one case), SLE (one case), and NSAID (one case). But the most common histological causes of end-stage renal diseases in primary NS were FSGS [two (40%) out of five patients], membranous nephropathy [two (14%) out of 14 patients], and crescentic nephritis (one patient only).

Proteinuria at the last follow-up

Primary NS: Resistant proteinuria occurred at the last follow-up in membranous nephropathy in one (7.1%) out of 14 patients and in membranoproliferative GN in one (5.9%) out of 17 patients. Partial remission occurred in membranoproliferative GN in 10 (58%) out of 17 patients, membranous nephropathy in six (42%) out of 14 patients, FSGS in two (40%) out of five patients, mesangial proliferative in one (14.3%) out of seven patients, and crescentic nephritis in the only patient presented with it, as shown in Fig. 3.

Secondary NS: Resistant proteinuria occurred at the last follow-up in amyloidosis in four (66%) out of six patients, in DM in five (37%) out of 15 patients, in hypertension in three (30%) patients out of 10, and in SLE in two (16%) out of 24 patients. Partial

Table 7 Relation between types of combination therapy and response

Types of treatment	Combination therapy response [*n* (%)]			Total
	Complete remission	Partial remission	Resistant	
Steroid+azathioprin	13 (48.10)	13 (48.10)	1 (3.70)	27 (100)
Steroid+cyclophosphamid	5 (71.40)	2 (28.50)	0	7 (100)
Steroid+azathioprin+cyclophosphamid	5 (55.50)	3 (33.30)	1 (11.10)	9 (100)
Steroid+cyclosporine	1 (100)	0	0	1 (100)
Total	24 (54.5)	18 (90.9)	2 (4.6)	44 (100)

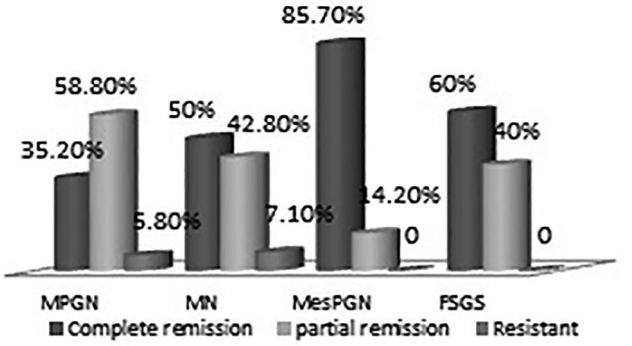
Table 8 Relation between renal function at last follow-up and etiology of nephrotic syndrome

Classification	*n* (%)			
	Normal	Received dialysis then stopping	On dialysis	Total
Primary	15 (65.20)	3 (13)	5 (21.70)	23 (10)
Secondary	15 (57.60)	2 (7.60)	9 (34.60)	26 (100)
Total	30 (61.20)	5 (10.20)	14 (28.50)	49 (100)

Table 9 Relation between proteinuria at last follow-up and etiology of nephrotic syndrome

Classification	Proteinuria at last follow-up [*n* (%)]			Total
	Complete remission	Partial remission	Resistant	
Primary	53 (66.25)	25 (31.25)	2 (2.5)	80 (100)
Secondary	16 (27.1)	28 (47.4)	15 (25.4)	59 (100)
Total	69 (49.6)	53 (38.1)	17 (12.2	139 (100)

Figure 3



Relation between renal function at the last follow-up and renal biopsy in primary NS. FSGS, focal segmental glomerulosclerosis; NS, nephrotic syndrome.

remission occurred in hypertension in seven (70%) patients, DM in eight (61%) patients, SLE in nine (37%) patients, amyloidosis in one (16%) patient, and in the two patients with myeloma, as shown in Table 9.

Discussion

A total of 139 patients (>12 years of age) presenting with NS were included in this study. The mean age of the patients was 33.9 ± 13.47 years. Male to female ratio was 1.3 : 1. There was a slight male preponderance, and this was similar to that in other studies, as reported by Tarik *et al.* [11]. The characteristics of our patients at presentation were similar to those reported previously in many studies [12–14]. Overall, 24.5% of the patients presented with hypertension, 37.4% with occasional microscopic hematuria, and 35% with impairment of renal function. In our study, older patients (>60 years at onset of NS) had a greater incidence of hypertension and severe impairment of renal function (64%); this was similar to the results obtained in a previous report [15]. In our study, the degree of hypoalbuminemia and severity of proteinuria were not affected by age. These results are in contrast with other studies on NS of childhood onset [16–18]; in these studies, children had more severe hypoalbuminemia than did patients in our study. In the present study, three out of 14 patients (21%) aged less than 60 continued on dialysis up to the end of the study (>60), six patients out of 30 (20%) in the age group 30–44 years continued on dialysis up to the end of the study, four patients out of 74 (5.4%) in the age group 12–29 continued on dialysis up to the end of the study, and one patient out of 21 (4.8%) in the age group 44–60 continued on dialysis up to the end of the study. Presentation with end-stage renal disease was almost confined to older adults, as was also reported in a study by White *et al.* [18], although a few children with end-stage renal disease have been described [19].

Out of 139 patients, 57.5% of them had idiopathic NS and the remaining 42.5% had secondary diseases. In the present study, the main cause of secondary diseases was SLE (in 17.2% patients); female predominance was noted mostly in young adults with an age range of 12–29 years. This is similar to the findings of others studies, as reported by Tarik *et al.* [11]. In addition, 9.35% of the patients in the present study were diabetic. Although worldwide the main cause of secondary NS is DM, in our study it was the second cause, probably due to the fact that in Egypt screening for proteinuria is not routinely carried out for diabetic patients. In addition, in Egypt, diabetic patients mostly present with end-stage renal disease. This may be attributed to relatively small number of cases, and a study on a large population can prove that to be right.

It is evident from the present study that membranoproliferative GN (30.5% of the patients) is the most common histological type of GN leading to NS. This is followed by membranous nephropathy (25.43% of the patients), mesangial proliferative GN (11.86% of the patients), amyloidosis (10.16% of the patients), FSGS (8.47% of the patients), diffuse proliferative GN (5.08%), focal proliferative, minimal mesangial, sclerosing GN, crescent GN (1.69% of the patients) and IgA nephropathy (1.69% of the patients). This is very similar to the pattern of glomerulopathy reported by a study from PIMS, Islamabad [20].

A study by Muzaffar [21] has reported that membranoproliferative GN is the leading cause of

glomerulopathy, followed by minimal change disease and FSGS, which is in agreement with the findings of this study. In a study conducted in Al Amiri renal center, Kuwait [22], FSGS has been reported to be the leading cause, followed by minimal change disease and IgA nephropathy.

Country/Area	Commonest histological pattern
USA [23–25]	Membranous nephropathy
UK [26]	IgA nephropathy
Middle East (Kuwait) [22]	FSGS
Pakistan	
Sindh [27]	FSGS
NWFP [9]	Mesengioproliferative GN
Punjab [28]	MCD
PGMI [29]	MCD
Peshawar [30]	Membranoproliferative GN
This study	Membranoproliferative GN

We found that membranoproliferative GN was seen mostly in middle-aged patients, with an age range of 30–44 years. Female predominance was noted (F : M ratio: 1.25 : 1); this was similar to the results reported in a study by Khan *et al.* [30]. The incidence of FSGS in our study was increased in young age group. Although the incidence of diffuse proliferative GN is decreasing in the developed countries because of better control of infection, as reported in a study by El-Reshaid *et al.* [22], in the developing countries, it is still a significant finding, as reported in a study by Palmieri *et al.* [25]. Only three patients (5.08%) in the present study had diffuse proliferative GN. This is similar to the findings of others studies, as reported in a study by Khan *et al.* [30].

Similar to other studies [9,22–31], our study in adult population, aged more than 44 years, revealed messangio-proliferative GN as the most frequently occurring glomerulopathy, followed by membranous nephropathy and tubulointerstitial nephritis. However, a study by Osmani and Farooqi [27] has reported, on the basis of renal biopsies from Jinnah Post Graduate Medical Institute, Karachi, FSGS to be the leading cause of glomerulopathy, followed by membranous and minimal change disease (MCD), whereas a study from Kuwait has reported FSGS as the most common cause of glomerulopathy, followed by MCD and IGA nephropathy. On the other hand, the present study showed membranous nephropathy to be the leading cause of glomerulopathy in patients more than 40 years of age, followed by messangio-proliferative GN.

In the present study, NS in one patient (1.6%) was due to IgA nephropathy, which is similar to the findings of a study conducted by Tarik *et al.* [11]. Although IgA nephropathy is the most common type of primary GN in many parts of the world, few patients present with NS. Most of them present with recurrent microscopic hematuria, preceded 1 or 2 days earlier by infections ('synpharyngitic nephritis'). A study by Qureshi *et al.* reported that 2.7% of the children with NS, aged less than 16 years, had IgA nephropathy [31], and another study conducted on 300 patients reported a 3% incidence of IgA nephropathy [32].

More importantly, the findings of deranged renal function in different entities show that almost all patients of FSGS, amyloidosis, focal proliferative GN, membranous nephropathy, and crescentic GN were associated with impaired renal functions. More than half of the cases (66.6%) with renal amyloidosis presented with impaired renal function. In this study, both mesangial proliferative GN and minimal mesangial GN were rarely associated with significant renal impairment. This is very similar to results of other studies [30].

In the present study, 2.1% patients presented with DVT and one patient presented with DVT and pulmonary embolism. The risk of DVT in our study was more than that of other studies. In a large retrospective study, the relative risk of DVT in patients with NS was 1.7 compared with those without NS, with an annual incidence of DVT of 1.5%, as reported in a study by Kendall *et al.* [33].

DVT mostly occurred in the first 6 months after diagnosis, which is similar to the findings of other studies [34].

The risk of pulmonary embolism in the present study was 1.4, and was especially high in persons in the age range 30–44 years; this is similar to the results obtained in a study by Mahmoodi *et al.* [35], which reported that the risk of pulmonary embolism was 1.4 and was especially high in patients in the age group 18–39 years (relative risk = 6.8).

In adults with the NS, arterial thrombosis (0.7%) is less common than venous thrombosis (2.1%). Only one patient had a myocardial infarction, but it is a serious complication causing morbidity, although there has been controversy challenging this claim in the past [36]. An increased risk for coronary events in patients with the NS has been documented in a retrospective, controlled study [37].

Hypertension with renal failure and anemia are features of more serious renal disease (e.g. FSGS, amyloidosis. membranoproliferative GN, and crescentic nephritis) rather than are other histological types; this finding is very similar to that of other studies, as reported by Gooden *et al.* [38].

In patients with the primary NS, on the basis of the therapeutic response to steroids in younger patients, 58% enter complete remission with disappearance of proteinuria during 8-week treatment. This is similar to the results obtained in others studies [16,39,40]. In contrast, 20% of our adult patients (age >30 years) achieved complete remission; this result was obtained in other studies [16,17], where a complete remission in 16 weeks was achieved. This slower response to treatment was not related to age at onset. This slower response of our adult-onset patients may represent an effect of lower corticosteroid dosage in relation to body size rather than a real difference in sensitivity to corticosteroids. Children usually receive about 60 mg/m^2/24 h for up to 4 weeks [39–41], which is equivalent to 100 mg/24 h or more for most adults.

Patients who responded rapidly to corticosteroids appeared to relapse earlier. The number of relapses in our older adult-onset population was lower than that reported for younger patients in other studies. Similar results were reported in a study by Siegel *et al.* [42]. The number of relapses was also lower with increasing age. Similar results were reported in a study by Zech *et al.* [43].

Reasons for the treatment with combination therapy were mostly to do with steroid resistance, occurrence of relapse while taking steroids, and occurrence of frequent relapses. Complete remission occurred in 26 (59%) out of 44 patients, partial remission occurred in 16 (36.6%) patients, and steroid resistance was detected in two (4.5%) patients. Combination therapy provides sustained remission of proteinuria and is also effective in the long-term preservation of renal function in patients with NS. Although our data are retrospective, they seem to suggest that a prolonged treatment with corticosteroids, immunosuppressive drugs, or cyclosporine may improve the renal outcome of patients with NS. Similar results were reported in a study by Griveas *et al.* [44].

Steroid and cyclophosphamid were the most effective combination therapy, which provides sustained remission of proteinuria and is also effective in decreasing the number of relapses.

In 24 patients with SLE, 95.8% of the patients were treated with combination therapy; overall, 86.7% of the group attained either complete or partial remission. Similar results were reported in a study by Ginzler *et al.* [45].

One patient was treated with steroid and azathioprin, and showed complete remission. The results of using steroid, azathioprin, and cyclophosphamid and using steroid and cyclophosphamid are nearly equal.

A series of well-performed randomized studies at the National Institutes of Health found that patients treated with cytotoxic agents had less renal failure at 10 years than did those treated with corticosteroids. Another controlled trial found that combination therapy with monthly cyclophosphamid along with methylprednisolone was more effective in preventing renal failure than was drug regimen alone, with no increased long-term side effects [45].

Amyloidosis (33.3%), hypertension (10%), and DM (7.7%) were the most common causes of end-stage renal diseases in patients with secondary NS. Similar results were reported in a study by Anwar *et al.* [9]. FSGS (for 40% of the patients), membranous nephropathy (for 14% of the patients), crescentic nephritis, and sclerosing GN were the most common histological causes of end-stage renal diseases in patients with primary NS. Similar results were reported in a study by Schmitz *et al.* [46].

FSGS, amyloidosis, membranous nephropathy, membranoproliferative GN, sclerosing GN, and crescentic nephritis are histological types that patients presented along with renal failure. In their study, Khan *et al.* [30] reported that the incidence of patients on dialysis increased in FSGS (40%), amyloidosis (33%), membranous nephropathy (14.8%), and crescentic nephritis (only patient presented with it) rather than in others histological types.

A total of 49 (35%) patients presented with renal insufficiency at the start of the present study; 23 (46.9%) of them had primary NS and 26 (53%) had secondary NS. At the end of the present study, 35 (71.5%) patients had normal renal function; 14 (28.5%) patients needed regular dialysis so that corticosteroid and cytotoxic agent could achieve good remission rate of the NS with preservation of long-term renal function.

Resistant proteinuria occurred at the last follow-up in amyloidosis (66%), membranous nephropathy (7.1%), and membranoproliferative GN (5.9). Partial remission occurred in membranoproliferative GN (58%), membranous nephropathy (42%), FSGS (40%), mesangial proliferative (14.3%), and crescentic nephritis (only patient presented with it).

Conclusion

It is evident from the present study that membranoproliferative GN is the most common histological type of GN, leading to NS. This is followed by membranous nephropathy, mesangial proliferative GN, amyloidosis, and FSGS.

Clinical features and biochemical values do not give many clues about the underlying histological types of GN. Therefore, we recommend that all patients with adult NS should undergo renal biopsy, as results permit us to establish a specific diagnosis, which helps in counseling the patients about the likely prognosis of their disease and to select a specific therapeutic regimen.

Hypertension with renal failure and anemia are features of more serious renal disease (e.g. FSGS, amyloidosis, membranoproliferative GN, and crescentic nephritis) rather than other histological types, and should warrant urgent nephrologists consultation for renal biopsy.

SLE was the most common underlying cause of secondary NS, followed by DM, hypertension, amyloidosis, and neoplasm (myeloma).

Steroid and cyclophosphamid were the most effective combination therapy, which provides sustained remission of proteinuria and is also effective in decreasing the number of relapses in steroid-resistant NS.

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Conflicts of interest
There are no conflicts of interest.

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