Clinical Report

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
2017, Vol. 45(6) 2139–2145

DOI: 10.1177/0300060517715339
journals.sagepub.com/home/imr
SAGE

Clinical characteristics and risk factors of severe infections in hospitalized adult patients with primary nephrotic syndrome

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Abstract

Objective: Infection is a common condition in patients with nephrotic syndrome. The objective of the present study is to investigate the clinical characteristics and risk factors of infections in adult patients with primary nephrotic syndrome (PNS).

Methods: Medical charts of 138 consecutive patients with PNS and infections who were admitted to hospital from April 2013 to April 2016 were systematically reviewed.

Results: Patients were divided into three groups according to the degree of infections: mild infection group (n = 45), moderate infection group (n = 60), and severe infection group (n = 33). In the severe infection group, most patients (96.9%) had pulmonary infections with opportunistic pathogens. There were significant differences in cumulative prednisone dose, immunosuppressor use, and CD4+ T cell count among the three groups. A lower CD4+ T cell count (<300 cells/mm^3) (odds ratio = 4.25 [95% confidence interval 1.680–10.98]) and higher cumulative dose of prednisone (odds ratio = 1.38 [95% confidence interval 1.05–3.26]) were risk factors for severe infections in adult patients with PNS.

Conclusions: CD4+ T cell count (<300 cells/mm^3) and a higher cumulative dose of prednisone are important risk factors for severe infections in adult patients with PNS.

Keywords

Infection, CD4+ T cell, adult patients, primary nephrotic syndrome, immunosuppression, kidney disease, transplantation

Date received: 28 February 2017; accepted: 24 May 2017

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Introduction

Infection is an important cause of morbidity and mortality in glucocorticoid-treated patients because of its immunosuppressive effects.[1,2] Many reports have estimated the clinical characteristics or risk factors of infections in kidney transplant recipients and those with rheumatic diseases.[3–6] However, little is known regarding this issue in patients with nephrotic syndrome (NS), especially adult patients with primary nephrotic syndrome (PNS).

Patients with NS have defective cell-mediated immunity.[7–9] Additionally, steroid or immunosuppressive therapy in patients with NS causes immunological dysfunction, which leads to increased susceptibility to infections.[10,11] Episodes of NS complicated by major infections usually require admission for aggressive treatment and affect patients' outcomes.[12–14] The present study was conducted to investigate the clinical characteristics and risk factors of severe infections in hospitalized adult patients with PNS.

Patients and methods

We retrospectively reviewed the inpatient medical records of patients with PNS who were complicated by infections and admitted to our hospital (First Affiliated Hospital of Wenzhou Medical University) from April 2013 to April 2016. All of the patients had electronic charts and the diagnosis codes were used.

PNS was defined as the presence of heavy proteinuria (>3.5 g/d) and hypoalbuminemia (<3.0 g/dL). Patients with lupus nephritis, allergic purpura nephritis, diabetic nephropathy, nephropathy of amyloidosis, and myeloma nephropathy were excluded. Patients were designated as having infectious complications if there were microbiologically or clinically documented infections confirmed by infectious disease specialists or nephrologists. Microbiologically-documented infections were defined as signs or symptoms of infection with an organism that was isolated by specimen culture (e.g., blood, urine, sputum, cerebrospinal fluid, and bronchoalveolar lavage fluid), antigen testing from blood, or histological material from a definite site of infection. Clinically documented infections were defined as fever accompanied by appropriate clinical findings, such as pulmonary infiltrates or inflammation of the skin or soft tissue.

The severity of infections was classified according to previous studies as severe, moderate, and mild. Severe infections included severe signs and symptoms, such as high fever (>39°C), breathing difficulty and confusion, unstable vital signs, and infections requiring intravenous antibiotics. Moderate infections included moderate signs and symptoms, such as moderate fever (>38°C), cough, yellow sputum, and crackles, stable vital signs, and infections requiring intravenous antibiotics. Mild infections included mild signs and symptoms, such as mild fever or no fever (<38°C), sore throat, coughing and stuffy nose, stable vital signs, and infection requiring only oral antibiotics.[11,15]

The medical records of these patients were further reviewed and the following information was obtained: sex, age, renal pathology, disease duration of NS (the time from initiation of NS to confirmation of infection), cumulative dose of prednisone (5 mg prednisone = 4 mg methylprednisolone), and immunosuppressors administered prior to infections in the last year, sites of infections, aetiology of infections, laboratory data (when infection was confirmed), prophylactic treatments (sulfamethoxazole and other antibiotics), and outcomes.

Variables are described as mean and standard deviation or proportion. ANOVA or the χ^2 test was used to compare differences among groups. Logistic regression analysis was performed to determine the risk factors for severe infections in patients with PNS. A P value of <0.05 was

considered statistically significant. All statistical analyses were performed using SPSS 17 (IBM, Cary, NC, USA).

Results

Overall, 138 patients with infections among 1202 patients with PNS in hospital were analysed. There were 45 patients in the mild infection group, 60 patients in the moderate infection group, and 33 patients in the severe infection group. The most common site of infections was pulmonary (72.4%), followed by the upper respiratory tract (12.3%), urinary tract (6.5%), soft tissue (3.6%), gastrointestinal tract (2.1%), and central nervous system (1.4%). In the severe infection group, most patients (96.9%) had pulmonary infections (Table 1).

The causative microorganisms in the 138 patients with PNS are shown in Table 2. In 51 patients, microorganisms were not found (among them, 15 patients had no specimen to be tested). Among the other 87 patients, *Klebsiella pneumoniae* was the most commonly identified in 17 (12.3%) patients, followed by Gram-negative bacillus (6.5%), *Tubercle bacillus* (6.5%), aspergillosis (5.7%), *Escherichia coli* (5.7%), and *Streptococcus pneumoniae* (5.7%). In the severe infection group, most microorganisms were opportunistic pathogens, including aspergillosis (24.2%), nocardiosis (18.1%), *Pneumocystis carinii* (9.0%), *Tubercle bacillus* (9.0%), and Cryptococcus (3.0%). We also investigated viral infections, such as cytomegalovirus infection, but no virus was isolated in any of the three groups.

Clinical characteristics of infections in patients with PNS are shown in Table 3. The mean age at presentation was 59.3 ± 14.8 years and the female-to-male ratio was 51:87. The mean duration of NS was 10.4 months (range: 0.2–240 months). The mean cumulative prednisone dose was 3.5 ± 5.0 g. Patients in the severe infection group had the most cumulative prednisone dose (7.1 ± 6.1 g) and this dose was significantly higher than that in the other two groups (2.9 ± 4.3 and 1.5 ± 3.5, $p = 0.013$). A total of 34.7% of patients had cyclophosphamide, mycophenolate mofetil, cyclosporine A, tacrolimus, or azathioprine therapy. Patients in the severe infection group had the highest use of immunosuppressors, and this use was significantly higher than that in the other two groups ($p = 0.029$).

All patients had a renal biopsy. The most common renal pathological types were membranous nephropathy (47.1%), followed by minimal change disease (34.0%), IgA nephropathy (10.1%), focal segmental glomerulosclerosis (7.9%), and mesangioproliferative glomerulonephritis (0.7%).

Table 1. Sites of infections in patients with PNS (n, %).

Infection sites	Mild infection (n = 45)	Moderate infection (n = 60)	Severe infection (n = 33)	Total (n = 138)
Pulmonary	23 (51.1)	45 (75.0)	32 (96.9)	100 (72.4)
Upper respiratory tract	17 (37.7)	0 (0)	0 (0)	17 (12.3)
Urinary tract	1 (2.2)	8 (13.3)	0 (0)	9 (6.5)
Soft tissue	2 (4.4)	3 (5.0)	0 (0)	5 (3.6)
Gastrointestinal tract	1 (2.2)	2 (3.3)	0 (0)	3 (2.1)
CNS	0 (0)	1 (1.6)	1 (3.0)	2 (1.4)
Others	1 (2.2)	1 (1.6)	0 (0)	2 (1.4)

PNS: primary nephrotic syndrome, CNS: central nervous system.

Table 2. Aetiology of infections in patients with PNS (n, %).

Aetiology	Mild infection (n = 45)	Moderate infection (n = 60)	Severe infection (n = 33)	Total (n = 138)
Klebsiella pneumoniae	7 (15.5)	9 (15.0)	1 (3.0)	17 (12.3)
Gram-negative bacillus	5 (11.1)	4 (6.6)	0 (0)	9 (6.5)
Tubercle bacillus	0 (0)	6 (10.0)	3 (9.0)	9 (6.5)
Aspergillosis	0 (0)	0 (0)	8 (24.2)	8 (5.7)
Escherichia coli	3 (6.6)	5 (8.3)	0 (0)	8 (5.7)
Streptococcus pneumoniae	4 (8.8)	4 (6.6)	0 (0)	8 (5.7)
Nocardiosis	0 (0)	0 (0)	6 (18.1)	6 (4.3)
Staphylococcus aureus	2 (4.4)	3 (5.0)	0 (0)	5 (3.6)
Pneumocystis carinii	0 (0)	0 (0)	3 (9.0)	3 (2.1)
Pseudomonas aeruginosa	1 (2.2)	2 (3.3)	0 (0)	3 (2.1)
Acinetobacter baumannii	0 (0)	2 (3.3)	0 (0)	2 (1.4)
Cryptococcus	0 (0)	1 (1.6)	1 (3.0)	2 (1.4)
Others	1 (2.2)	6 (10.0)	0 (0)	7 (5.0)
No isolate	22 (48.8)	18 (30.0)	11 (33.3)	51 (36.9)

PNS: primary nephrotic syndrome.

The mean 24-h urine protein level was 5.9 ± 5.1 g/day. Albumin levels dramatically declined over the course of infection and the mean value was 20.3 ± 5.6 g/L. Serum creatinine levels were increased and the mean value was 142.1 ± 138.4 μmol/L. Immunoglobulin G (IgG) levels were declined and the mean value was 7.1 ± 3.7 g/L. The mean cholesterol level was 7.1 ± 3.0 mmol/L. Patients in the severe infection group had a significantly lower cholesterol level compared with the other two groups ($p = 0.023$). Patients in the severe infection group had lower 24-hour protein levels and higher albumin and IgG levels, but there were no significant differences among the three groups. The CD4+ T cell count decreased over the course of infection and the mean level was 436.6 ± 213.6 cells/mm^3. Patients in the severe infection group had a significantly lower CD4+ T cell count compared with the other two groups ($p = 0.017$).

The rate of complications, including diabetes mellitus and chronic pulmonary disease, which could increase the opportunity of infections, was not significantly different among the three groups. Six patients died, and all of these patients were in the severe infection group. The mortality rate among the three groups was significantly different ($p < 0.001$).

Logistic regression showed that a lower CD4+ T cell count (<300 cells/mm^3) (odds ratio = 4.25 [95% confidence interval 1.680–10.98], $P < 0.001$) and a higher cumulative dose of prednisone (odds ratio = 1.38 [95% confidence interval 1.05–3.26], $P = 0.015$) were risk factors for severe infections in patients with PNS.

Discussion

In this study, we describe the clinical characteristics of infections in a Chinese cohort of adult patients with PNS and identified the possible risk factors associated with severe infections. Most previous studies of NS complicated by infections focussed on children. Ajayan et al.[14] found that the incidence of major infections was 36.6% in hospitalized children with NS and the most common major infection was peritonitis

Table 3. Clinical characteristics of infections in patients with PNS.

Variables	Mild infection (n = 45)	Moderate infection (n = 60)	Severe infection (n = 33)	Total (n = 138)	*P* value
Sex (female:male)	18:27	24:36	9:24	51:87	0.748
Age (years)	55.0 ± 15.3	60.5 ± 14.8	63.0 ± 14.2	59.3 ± 14.8	0.364
PNS duration (months)	9.7 ± 15.3	10.5 ± 18.7	11.2 ± 12.7	10.4 ± 16.4	0.347
Cumulative dose of prednisone (g)	1.5 ± 3.5	2.9 ± 4.3	7.1 ± 6.1	3.5 ± 5.0	0.013*
[a]Immunosuppressant therapy (%)	6 (13.3)	21 (35.0)	21 (63.6)	48 (34.7)	0.029*
Histological subtype					0.443
MN	23 (51.1)	29 (48.3)	13 (39.3)	65 (47.1)	
MCD	14 (31.1)	22 (36.6)	11 (33.3)	47 (34.0)	
IgA nephropathy	6 (13.3)	3 (5.0)	5 (15.1)	14 (10.1)	
FSGS	2 (4.4)	6 (10.0)	3 (9.0)	11 (7.9)	
MPGN	0 (0)	0 (0)	1 (3.0)	1 (0.7)	
24-h urine protein (g/day)	6.4 ± 2.9	6.8 ± 6.6	3.6 ± 3.6	5.9 ± 5.1	0.225
Albumin (g/L)	19.1 ± 3.7	19.3 ± 5.7	23.6 ± 6.6	20.3 ± 5.6	0.076
Scr (μmol/L)	135.0 ± 41.6	165.4 ± 131.5	166.2 ± 152.3	142.1 ± 138.4	0.292
IgG (g/L)	7.7 ± 3.6	5.9 ± 2.4	8.4 ± 5.2	7.1 ± 3.7	0.155
Cholesterol (mmol/L)	8.1 ± 2.6	7.4 ± 3.1	5.2 ± 1.5	7.1 ± 3.0	0.023*
CD4 + cell count (cells/mm^3)	533.4 ± 204.5	411.4 ± 200.7	296.7 ± 185.7	436.6 ± 213.6	0.017*
[b]Complications	3 (6.6)	18 (30.0)	9 (27.2)	30 (21.7)	0.223
[c]Prophylactic treatments	5 (11.1)	9 (15.0)	5 (15.1)	19 (13.7)	0.820
Mortality (%)	0 (0)	0 (0)	6 (18.1)	6 (4.3)	<0.001*

PNS: primary nephrotic syndrome; MN: membranous nephropathy;
MCD: minimal change disease; FSGS: focal segmental glomerulosclerosis; MPGN: mesangioproliferative glomerulonephritis;
Scr: serum creatinine;
IgG: immunoglobulin G.
[a]Including cyclophosphamide, mycophenolate mofetil, cyclosporine A, tacrolimus, and azathioprine.
[b]Including diabetes mellitus, chronic pulmonary disease (chronic obstructive pulmonary disease), and bronchiectasis.
[c]Including sulfamethoxazole and other antibiotics.
Data are shown as mean ± SD (standard deviation) or percentages.
*$p < 0.05$.

(incidence of 13.8%). Wei et al. showed that 97 of 508 (19.1%) admissions were associated with defined major infections in children with NS.[16] Makoto et al.[10] reported infectious episodes in 16 (19%) adult patients with NS during the study period, and bacterial infections were the most common, occurring in 10 of 16 (63%) patients. In our study, infections were found in 11.4% of patients with PNS in hospital, and the most common site of infections was pulmonary (72.4%) and the most common microorganism was *Klebsiella pneumoniae* (12.3%). In the severe infection group, most (96.9%) patients had pulmonary infections with opportunistic pathogens, including aspergillosis, nocardiosis, *Pneumocystis carinii*, *Tubercle bacillus,* and Cryptococcus.

An interesting finding in our study was that patients in the severe infection group had lower 24-h urine protein and cholesterol

levels, and higher albumin and IgG levels than those in the other two groups. These findings are not consistent with previous studies. Ogi et al.[10] found that hypogammaglobulinaemia and renal insufficiency were independent risk factors for bacterial infection in adult patients with NS. Elidrissy reported six nephrotic children with peritonitis and two with pneumococcal meningitis. All of these cases had hypoproteinaemia and all of those tested had low plasma IgG levels.[17] Gulati et al.[18] showed that children with NS who developed infectious complications had significantly higher serum cholesterol levels and lower serum albumin levels than children with NS without infection. However, in our study, many patients (39.1%) were not under corticosteroid therapy, mainly because infection occurred before steroid use. These patients were all in the mild and moderate infection groups. Therefore, after a long time of immunosuppressive therapy, the status of NS tends to be better in patients with severe infection. These findings suggested that hypoproteinaemia and hypogammaglobulinaemia were not the cause of severe infections in our patients.

Patients in the severe infection group had a longer duration of NS, larger cumulative dose of prednisone, more immunosuppressor use, and lower CD4+ cell count. Glucocorticoids exert many complex, qualitative, immunosuppressive effects that induce cellular immunodeficiency, and increase host susceptibility to types of opportunistic infections. Glucocorticoids also rapidly cause redistribution of lymphocytes from the circulation, depleting circulating CD4+ T cells, and to a lesser extent, CD8+ T cells.[19] Different studies have demonstrated that steroid therapy increases the susceptibility for infections because of impairment of cellular immunity.[19–21]

In the present study, we found two important risk factors for severe infections in patients with PNS. These factors were a larger cumulative dose of prednisone and a lower CD4+ cell count. This finding is consistent with previous studies on kidney transplant recipients and those with rheumatic diseases.[3–6,22,23] Fernández-Ruiz et al.[4] showed that monitoring of peripheral blood lymphocyte subpopulations effectively identified kidney transplant recipients at risk of opportunistic infections. Calarota et al.[22] considered that determination of T-lymphocyte subsets was a simple and effective parameter for identifying heart and kidney transplant recipients at risk of developing opportunistic infections. Another study showed that monitoring of T-helper cell counts may be useful for estimating the risk for subsequent infections in patients with various chronic inflammatory diseases.[23]

In conclusion, this study showed that, in the severe infection group, albumin and IgG levels were higher than those in the other two groups, mainly because the status of NS tended to be better with immunosuppressive therapy. CD4+ T cells were lower in the severe infection group than in the other two groups because of immunosuppressive effects of glucocorticoids or immunosuppressors. Therefore, a decline in CD4+ T cells could be a risk factor for predicting severe infections in adult patients with PNS.

Declaration of conflicting interest

The Authors declare that there is no conflict of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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