RESEARCH BRIEF

Clinical Spectrum and Predictive Risk Factors of Major Infections in Hospitalized Children with Nephrotic Syndrome

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Received: October 15, 2012;
Initial review: November 26, 2012;
Accepted: January 04, 2013.

This observational study was conducted with the primary objective of studying the incidence of major infections in nephrotic syndrome (NS), while the secondary objectives were to evaluate the risk factors for and the etiological spectrum of major infections. Eighty six children up to 13 years of age fulfilling the International Study of Kidney Disease in Children (ISKDC) criteria for NS, who required 101 hospital admissions were recruited from November 2010 to July 2012. Major infections were defined as those that are disseminated, affecting deep organs, requiring hospitalization or potentially life-threatening. The incidence of major infections was 36.6%. Among the major infections, peritonitis and pneumonia together accounted for 72.9%, while urinary tract infections and cellulitis accounted for 16.2%. On logistic regression, severe ascites and more severe clinical types of NS independently predicted major infections, while serum cholesterol >400 mg/dL was the sole predictor of peritonitis.

Keywords: *India, Nephrotic syndrome, major infections, peritonitis.*

Children with nephrotic syndrome (NS) are exposed to multiple infectious complications resulting in significant mortality and morbidity [1,2]. There is paucity of literature regarding the clinical spectrum of major infections in childhood NS from developing countries in recent years. Knowledge of these parameters has therapeutic and preventive relevance [2]. We, therefore, conducted the present study.

METHODS

This prospective study was conducted from November 2010 to July 2012 at a tertiary hospital, and was approved by the Institutional ethics committee. The primary objective was to study the incidence of major infections in NS, while secondary objectives were to evaluate (*a*) the risk factors for major infections and (*b*) their etiological spectrum. Children below 13 years of age, fulfilling ISKDC diagnostic criteria for NS [3-5] were included if hospitalization was required for: major infections, severe anasarca, shock, seizures, thrombosis, unconsciousness, respiratory distress, tetany, or for renal biopsy.

The incidence of major infections in NS was estimated as 35% [2,6,7]. Assuming 10% variation with 95% confidence, sample size for estimating incidence of major infections was 88. Results were analyzed with SPSS version16, using Student *t*-test, Chi square test or Fisher exact test. Logistic regression was used to analyse predictors of major infections and peritonitis.

Major infections were defined as disseminated, affecting deep organs, requiring hospitalization (*e.g.* cellulitis, disseminated varicella) or potentially life-threatening [8]. Specific major infections were defined as follows:

(1) *Peritonitis*: Abdominal pain, tenderness, distension, diarrhea, or vomiting, with ascitic fluid >100 leukocytes/mm^3 and minimum 50% neutrophils and/or positive culture [3,9,10].

(2) *Pneumonia*: fast breathing and chest indrawing with chest *X*-ray confirmation [1].

(3) *Urinary tract infection (UTI):* Bacterial colony count of >10^5 organisms/mL in a clean-catch midstream urine sample with fever (>38.5°C), dysuria or increased urination frequency [1].

(4) *Cellulitis*: Erythema, warmth, swelling, fever and local tenderness in any body part.

(5) *Meningitis*: Fever and one of the following: neck rigidity, altered sensorium, seizures, with confirmation by cerebrospinal fluid cytology, biochemistry and culture.

Severe ascites was defined as tense ascites or ascites with dyspnea. Generalized edema (including scrotal edema, vulval edema or severe ascites) was considered as severe anasarca. Frequently relapsing (FRNS), steroid dependent (SDNS), steroid resistant (SRNS) or infrequently relapsing NS (IFRNS) were considered as 'more severe clinical types of NS'.

NS was investigated and managed as per Indian Pediatric Nephrology Group guidelines [3]. Blood and urine cultures; and peritoneal, pleural or cerebrospinal fluid analysis and culture were done when clinically indicated.

RESULTS

86 children with NS, requiring 101 hospitalizations, were recruited. Peritonitis and pneumonia accounted for 27 out of the 37 children with major infections (72.9%) (***Table I***). Urine cultures were sent in 10 cases (3 had UTI); while ascitic tap was performed in 20 (14 had peritonitis). The infectious agents included *E.coli* (2 cases) and *Klebsiella* (1 case) in UTI, Pneumococcal peritonitis (1 case), Methicillin Resistant *Staphylococcus aureus* (MRSA) in cellulitis and osteomyelitis (1 each), and *Pseudomonas* in cellulitis (1 case). One child with SRNS (having chronic glomerulonephritis) died of pneumonia. Children aged >4 years constituted 78.6% of peritonitis, while duration of NS >2 years constituted 64.3% of peritonitis. The mean age of children with peritonitis was 7.9 ± 3.3 years, whereas mean age of children with pneumonia was 6.4 ± 3.1 years.

***Web Table* I** depicts predictors of peritonitis on univariate analysis. On logistic regression, hypercholesterolemia >400 mg/dL independently predicted peritonitis (OR = 6.89 (1.30 – 36.43), P = 0.023).

Predictors for major infections on logistic regression were 'more severe clinical types of NS' when compared to first episode of NS, *i.e.* IFRNS [OR 9.94 (2.56 -38. 67), P< 0.01], FRNS [OR 28.19 (3.73- 212.28) , P< 0.01], SDNS [OR 25.84 (2.89-231.1), P< 0.01], SRNS [OR 4.9 (2.56 -38. 67), P=0.033]; and severe ascites [OR 0.15(0.05-0.49), P< 0.01].

DISCUSSION

In our study, major infections constituted 36.6% of the subjects. Other studies reported incidence ranging from 32% to 38% [2,7]. The commonest major infection was peritonitis (13.8% incidence), as compared to 1.4% to 16% in other studies [1,2,7,11,12]. Ascitic fluid culture was positive in only 1 patient. Eleven of the 14 cases with peritonitis were initially seen by general practitioners who prescribed antibiotics. These were ineffective but

TABLE I CLINICAL AND BIOCHEMICAL PROFILE OF STUDY SUBJECTS (AMONG 101 HOSPITAL ADMISSIONS *)

Characteristics	*Value*
Age (y)	6.8 ± 3.5
Duration of nephrotic syndrome (y)#	1.9 ± 1.7
Duration of edema before presentation (wks)	2.8 ± 2.4
Sex (male)	53 (52.5)
Pneumococcal vaccine received	6 (5.9)
Major infections, n(%)	37 (36.6)
Spontaneous bacterial peritonitis	14 (37.8)
Pneumonia	13 (35.1)
Urinary tract infection	3 (8.1)
Cellulitis	3 (8.1)
Osteomyelitis	1 (2.7)
Disseminated varicella	1 (2.7)
Herpes zoster	1 (2.7)
Meningitis	1 (2.7)
Clinical type of nephrotic syndrome	
1st episode	45 (44.6)
IFRNS	21 (20.8)
FRNS	9 (8.9)
SDNS	7 (6.9)
SRNS	19 (18.8)
Severe ascites	62 (61.4)
Scrotal edema (among 53 males)	20 (37.7)
Vulval edema (among 48 females)	16 (33.3)
Past history of major infections #	18 (17.8)
Immunosuppressants received	
Prednisolone only	84 (83.3)
Levamisole with prednisolone	6 (5.9)
Cyclophosphamide with prednisolone	3 (2.9)
Cyclosporine with prednisolone	8 (7.9)
Histopathology (among 12 renal biopsies)	
Focal segmental glomerulosclerosis	3 (25)
Mesangioproliferative glomerulonephritis	4 (33.3)
Minimal change disease	2 (16.7)
C3 nephropathy	1 (8.3)
IgA nephropathy	1 (8.3)
Chronic glomerulonephritis	1 (8.3)
Death	1 (0.9)
Serum albumin (g/dL)	2.1 ± 0.6
Serum cholesterol (mg/dL)	419.8 ± 128.1
Blood urea (mg/dL)	35.2 ± 28.1
Serum creatinine (mg/dL)	0.7 ± 0.6
Spot urine protein: creatinine ratio	2.89 ± 0.3
GFR (mL/m^2/min)(Schwartz formula)	112.2 ± 75.9

** Indications for hospitalization included severe anasarca – 55 cases (including 11 with scrotal edema), major infections- 37 (one case of pneumonia presented with shock), renal biopsy- 6, tetany -2 and seizures- 1 case. #These included peritonitis in 9, UTI in 6, pneumonia in 2 and cellulitis in 1 case, All values in no. (%) and mean* ± SD.

probably contributed to low ascitic fluid culture positivity [2]. Pneumonia was the second commonest infection in the subjects (12.9%), as compared to 3.9% to14% in Indian studies [1,2]. UTI was relatively uncommon in our subjects. In consonance with our observations, Srivastava, *et al*. [7] reported no episodes of UTI in their study. In other studies, UTI incidence ranged from 13.7% to 46% [1]. These variations probably reflect geographical or socioeconomic heterogeneity of patient populations.

Peritonitis in NS has been usually described to occur within initial few years after diagnosis and in younger children [6,13,14]. Our results; however, indicate that irrespective of age or increasing duration of disease (probably related to multiple relapses) [1,2,7,13,14], major infections prevail in NS. Immunosuppressive agents did not predict major infections, as in some studies [2,6], suggesting that the origin of infections in NS is far more complex and multifactorial.

Hypercholesterolemia >400 mg/dL was a risk factor for peritonitis. Hypercholesterolemia may have a direct pathophysiological role as hypercholesterolemic serum inhibits lymphocyte proliferation in response to antigen stimulation [15] Secondly, hypercholesterolemia is an indirect consequence of hypoalbuminemia which has been mentioned as a predictor of peritonitis in NS [2,13].

The merits of our study include prospective design, and a large sample size. Our study also has limitations. Due to resource constraints, detailed pathophysiological investigations were not undertaken. Secondly, although the predictors for major infections and peritonitis were analyzed, this study is not powered enough for the same.

Our hospital caters to patients of low socioeconomic status, which explains poor coverage of pneumococcal vaccination (6%). Improving pneumococcal vaccination coverage in NS could be a potentially important strategy to decrease the incidence of major infections. In the presence of hypercholesterolemia >400 mg/dL, an aggressive search for serious infections is essential along with prompt and aggressive antibiotic therapy.

Contributors: PA, SK and NB: were involved in management of the patients; PA: collected the data, reviewed the literature and drafted the manuscript; SK: conceptualized the study, reviewed the literature and critically reviewed the manuscript; NB: also critically reviewed the manuscript; JM: supervised the laboratory tests. All authors contributed to writing the paper and approved the final version of the manuscript and SK: shall act as guarantor of the paper.
Funding: None; *Competing interests:* None stated.

REFERENCES

1. Alwadhi RK, Mathew JL, Rath B. Clinical profile of children with nephrotic syndrome not on glucocorticoid therapy, but presenting with infection. J Paediatr Child Health. 2004;40:28–32.
2. Gulati S, Kher V, Gupta A, Arora P, Rai PK, Sharma RK. Spectrum of infections in Indian children with nephrotic syndrome. Pediatr Nephrol. 1995;9:431-4.
3. Indian Pediatric Nephrology Group, Indian Academy of Pediatrics, Bagga A, Ali U, Banerjee S, Kanitkar M, Phadke KD, *et al.* Management of steroid sensitive nephrotic syndrome: revised guidelines. Indian Pediatr. 2008;45:203-14.
4. Early identification of frequent relapsers among children with minimal change nephrotic syndrome. A report of the International Study of Kidney Disease in Children. J Pediatr. 1982;101:514-18.
5. Kher KK. Urinalysis. *In*: Kher KK, Makker SP *ed*. Clinical Pediatric Nephrology 1st edn. New York: McGraw-Hill, 1992. p. 186-8.
6. Senguttuvan P, Ravanan K, Prabhu N, Tamilarasi V. Infections encountered in childhood nephrotics in a pediatric renal unit. Indian J Nephrol. 2004;14:85-8.
7. Srivastava RN, Mooudgil A, Khurana O. Serious infections and mortality in nephrotic syndrome. Indian Pediatr. 1987;24:1077-80.
8. Irastorza GR, Olivares N, Arruza IR, Berriotxoa AM, Egurbide MV, Aguirre C. Predictors of major infections in systemic lupus erythematosus. Arthritis Res Ther. 2009;11:R109.
9. Wei CC, Yu IW, Lin HW, Tsai AC. Occurrence of infection among children with nephrotic syndrome during hospitalizations. Nephrology (Carlton). 2012;17:681-8.
10. Bagga A, Srivastava RN. Nephrotic syndrome. *In*: Srivastava RN, Bagga A. Pediatric Nephrology. 5th *ed*. New Delhi: Jaypee; 2005. p. 195 -234.
11. Gorensek MJ, Lebel MH, Nelson JD. Peritonitis in children with nephrotic syndrome. Pediatrics. 1988; 81:849-56.
12. Feinstein EI, Chesney RW, Zelikovic I. Peritonitis in childhood renal disease. Am J Nephrol. 1988; 8:147–65.
13. Hingorani SR, Weiss NS, Watkins SL. Predictors of peritonitis in children with nephrotic syndrome. Pediatr Nephrol. 2002;17:678-82.
14. Uncu N, Bulbul M, Yildiz N. Primary peritonitis in children with nephrotic syndrome: results of a 5-year multicenter study. Eur J Pediatr. 2010;169:73-6.
15. Anderson S, Garcia DL, Brenner BM. Renal and systemic manifestations of glomerular disease. *In*: Brenner BM, Rector FC Jr, eds. The kidney. 4th ed. Philadelphia: Saunders; 1991. p. 1831-70.