Pediatr Nephrol (1997) 11: 148–152

Pediatric Nephrology

Original article

Infections in infants with congenital nephrosis of the Finnish type

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Received March 25, 1996; received in revised form and accepted July 30, 1996

Abstract. The incidence and type of infections were retrospectively analyzed in 21 infants with congenital nephrosis of the Finnish type (CNF). During the median follow-up time of 1.1 years the infants suffered from 63 verified and 62 suspected episodes of sepsis. These accounted for half of all infections recorded. Forty percent of bacteremias were caused by coagulase-negative staphylococci, 16% were caused by *Staphylococcus aureus*, 17% were streptococcal, and 24% were caused by Gram-negative bacteria. One infant died of pleural empyema, but otherwise the outcome of infections was good. The use of central venous lines tended to increase the rate of staphylococcal bacteremias but had no significant effect on the overall incidence of infections. Prophylactic use of antibiotics did not reduce the incidence of septic or other infections. Infants with CNF had low levels of serum IgG, but prophylactic immunoglobulin infusions (0.5–1.0 g once or twice a week) did not reduce the frequency of infections, probably because the infused IgG was quickly lost into the urine. The results indicate that infants with CNF often suffer from septic infections associated with the invasive treatment modalities. Parenteral antibiotics covering the hospital strains of bacteria (especially staphylococci) should be started without delay when a nephrotic patient is not doing well.

Key words: Congenital nephrosis – Infections – Antibiotic prophylaxis – Immunoglobulin prophylaxis

Introduction

Congenital nephrotic syndrome of the Finnish type (CNF) is a hereditary disease occurring sporadically around the world. In Finland it is fairly common, with an incidence of 1 per 8,000 live births [1]. The disease manifests itself with massive proteinuria leading to edema and ascites during the first weeks of life [2]. Without treatment most patients die in early infancy. The treatment in Finland consists of three stages [3, 4]. First, aggressive protein supplementation and nutritional support is started as soon as nephrosis is noticed. Second, bilateral nephrectomy is performed and peritoneal dialysis is commenced at the age of about 1 year. Third, after some months on dialysis the children undergo kidney transplantation which is a curative treatment for CNF [3].

Infections are a major problem in children with nephrosis [5]. This is true also in infants with congenital nephrotic syndrome (CNS). In a report of Mahan et al. [6], 35 of 41 children with CNS suffered from severe bacterial infections and these were the cause of death in 88% of the patients. Similarly, one-third of the infants with CNF born in Finland from 1965 to 1973 died of infections [7]. In nephrosis the sensitivity to infections is believed to be due to the immunoglobulin and complement deficiency caused by severe protein loss [8, 9]. Nephrotic children are reported to be especially prone to infections caused by bacteria with capsules (pneumococcus, *Haemophilus influenzae*, meningococcus) [10].

We studied the incidence, type, and etiology of infections in 21 CNF infants during the nephrotic stage. Also, the effect of two major prophylactic measurements, immunoglobulin and antibiotic prophylaxis, was analyzed.

Patients and methods

The study was carried out at the Children's Hospital, University of Helsinki, Finland. The data from patient records were also collected at five central hospitals treating the patients. The study protocol was approved by the Institutional Review Board.

Twenty-one infants with CNF (13 boys, 8 girls) born in Finland during 1985–1988 were included in this study. CNF was diagnosed soon after birth on clinical grounds, excluding other causes of CNS. The diagnosis was histologically confirmed at nephrectomy in all children.

The therapy of nephrosis included daily albumin infusions, oral protein supplementation, and nutritional support [3, 4]. Albumin was

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Table 1. Infections in 21 infants with congenital nephrotic syndrome of the Finnish type (CNF) during nephrosis[a]

Infection	Total no. (%)	Frequency[b]	Comments
Sepsis[c]	64 (25)	2.5 (0–5.5)	Verified bacteremia and clinical signs of sepsis, treated with parenteral antibiotics
Suspected sepsis	62 (25)	2.5 (0–4.7)	Clinical signs of sepsis, parenteral antibiotic treatment, blood culture negative
Focal bacterial infection	53 (21)	2.2 (0–4.7)	Acute otitis media 31, conjunctivitis 6, skin infection 6, urinary tract infection 5, pneumonia 3, tonsillitis 1, catheter infection 1
Viral infection	57 (23)	2.3 (0–6.0)	Upper respiratory tract infection 31, gastroenteritis 24, varicella 2
Mucocutaneous yeast infection	16 (6.3)	0.7 (0–6.0)	Stomatatis, skin infection or both
Total	252 (100)	10.2	

[a] The median and cumulative follow-up times were 1.12 and 24.5 years
[b] The mean number of episodes/patient year (range)
[c] Including 2 candidemias

infused at night and the children stayed in hospital or spent the day at home. All invasive procedures were performed by experienced personnel on the wards.

For the intravenous infusions and blood sampling two types of central venous catheters were used. First, there were the cuffed, tunnelled silicone elastomer catheters of Hickman-Broviac type with one lumen (Corcath, Cormed, Medina, New York, USA) and secondly, totally implanted venous access chamber systems (Chemoport, HDC Corporation, Mountain View, Calif., USA). All catheters were inserted in the operating room with strict aseptic techniques.

Eleven CNF children received antimicrobial prophylaxis for a total of 11.1 patient years. Fourteen children received intravenous gammaglobulin (Sandoglobulin, Sandoz, Basel, Switzerland) infusions for various periods of time as a prophylaxis for infections.

The clinical data were collected from the patient records. The timing, quality, and etiology of the infections as well as therapy were recorded. The infection episodes were divided into five categories as shown in Table 1. If a child had two or more types of infection at the same time (e. g., viral respiratory tract infection and middle ear infection), the episode was named according to the major problem (e. g., middle ear infection).

Because the infections were not normally distributed among the children, median values and ranges were used. In comparison of the treatment modalities, the relative incidence of infections was based on the number of infection episodes per year per patient. Statistical analysis was performed by non-parametric, two-directional Kendall's S-test [11].

Results

The 21 children with CNF suffered from 251 recorded infection episodes during the nephrotic period (median follow-up 1.12 years, range 0.11–3.92 years) (Table 1). The

Table 2. The etiology of 64 septic episodes in 21 CNF children during nephrosis[a]

Pathogen	Total	Central venous catheter		Antibiotic prophylaxis		Gammaglobulin prophylaxis	
		No	Yes	No	Yes	No	Yes
Gram-positive bacteria	49 (73)[b]	10	39	28	21	33	16
Staphylococcus epidermidis	27 (40)	4	23	10	17	15	12
Staph. aureus	11 (16)	3	8	9	2	10	1
Streptococcus pneumoniae	6 (9.0)	2	4	6	–	4	2
Other streptococci	5 (7.5)[c]	1	4	3	2	4	1
Gram-negative bacteria	16 (24)	6	10	6	10	7	9
Escherichia coli	8 (12)	5	3	3	5	3	5
Other coliforms	5 (7.5)[d]	1	4	3	2	1	4
Pseudomonas sp.	2 (3.0)	–	2	–	2	2	–
Acinetobacter	1 (1.5)	–	1	–	1	1	–
Yeasts							
Candida albicans	2 (3.0)	–	2	1	1	1	1
Total	67 (100)	16	51	36	31	41	26

[a] In 3 episodes two pathogens were cultured
[b] No of positive cultures (%)
[c] *Strep. pyogenes* (1), *Strep. faecalis* (3), *Strep. salivairius* (1)
[d] *Enterobacter* (2), *Serratia* (2), *Klebsiella* (1)

Table 3. Number and incidence of infections in CNF children with and without indwelling central venous catheters

	No catheter	Hickman-Broviac	Chemoport
No. of children	21	15	12
No. of catheters	–	39	25
Patient years	9.6	5.3	9.5
Sepsis	1.7 (16)[a]	3.4 (18)	3.0 (29)
Suspected sepsis	2.7 (26)	2.6 (14)	2.3 (22)
Focal bacterial infection	2.8 (27)	2.0 (11)	1.6 (15)
Viral infection	2.0 (19)	1.7 (9)	3.0 (29)
Superficial yeast	0.7 (7)	0.6 (3)	0.6 (6)
Total	9.9 (95)	10.1 (54)	10.5 (100)

[a] Infection episodes per patient year (no. of episodes)

incidence varied between children, from 5.2 to 20 infections per patient year (median 13.1). Age did not affect the appearance of infections. Septic and other infections occurred with a similar frequency throughout the 1st year. The outcome of infections was in general good. Of the 21 patients, 1 died of lung empyema at the age of 7 months.

Sixty-four episodes of verified bacterial sepsis were diagnosed with an average of 2.5 episodes per patient year (range 0–5.5) (Table 1). The major pathogens were coagulase-negative staphylococci, *Staphylococcus aureus*, and streptococci (Table 2). Gram-negative bacteria accounted for 22% of the episodes. Two episodes of candidemia were diagnosed. Sepsis was suspected on 62 occasions where blood cultures remained negative (Table 1). All these episodes were treated with parenteral antibiotics. The frequency of verified and suspected sepsis was not evenly distributed between the patients and ranged between 0.65 and 12.0 episodes per patient year. Acute middle ear infection was the most common focal bacterial infection (Table 1).

All except 1 child had an indwelling venous catheter (Hickman-Broviac or Chemoport) at some time during nephrosis. Overall, 64 catheters were used in the 20 children. The incidence of verified septic episodes tended to be higher during the time the child had a central venous catheter (2.9–3.2 episodes per patient year) compared with the period when only a peripheral vein catheter was in use (1.7 episodes per patient year), but this difference was not statistically significant (Table 3). No difference was found between the two types of central venous catheters.

Forty-five percent of the bacteremias in children with central venous catheters were caused by coagulase-negative staphylococci, compared with 25% in children with peripheral vein catheters (Table 2). Of the 26 bacteremias (85%) caused by *Staph. epidermidis*, 22 occurred in patients with a central venous catheter.

Eleven CNF children received antimicrobial prophylaxis for a total of 11.1 patient years. If this period was compared with the time (13.4 patient years) without any prophylaxis, no difference was seen in the incidence of infections (Table 4). The children had in total 30 and 31 episodes of sepsis with and without prophylaxis, respectively. The major difference in the etiology was that all pneumococcal bacteremias occurred in children without prophylaxis (Table 2). In contrast, the proportion of bacteremias caused by coagulase-negative staphylococci was higher during the prophylaxis.

Serum IgG levels in CNF children during the nephrotic period were on average less than one-tenth of the normal values. Serum IgA levels, however, were relatively normal, while serum IgM levels increased sharply during the 1st month of life and were clearly elevated thereafter (Fig. 1). Because of the decreased serum IgG concentration, 14 children received gammaglobulin (Sandoglobulin) infusions for various periods of time as a prophylaxis for infections (Table 5). However, no prophylactic effect was seen in the incidence of any type of infections. The pathogens responsible for bacteremias were also similar (Table 2).

Table 4. Number and incidence of infections in CNF children with and without antimicrobial prophylaxis

	No antibiotic	Antibiotic[a]
No. of children	21	11
Patient years	13.4	11.1
Sepsis	2.4 (32)[b]	2.8 (31)
Suspected sepsis	2.5 (34)	2.5 (28)
Focal bacterial infection	2.4 (32)	1.8 (20)
Viral infection	2.0 (27)	2.5 (28)
Superficial yeast infection	0.7 (10)	0.5 (6)
Total	10.2 (137)	10.1 (112)

[a] The antibiotics were: phenoxymethylpenicillin (orally) or benzylpenicillin (parenterally) alone (5.6 years), combination of intramuscular benzylpenicillin and oral co-trimoxazole (3.6 years), co-trioxazole alone (1.7 years) and phenoxymethylpenicillin with nitrofurantoin or trimethoprim (0.2 years)

[b] Infection episodes per patient year (no. of episodes)

Table 5. Number and incidence of infections in CNF children with and without gammaglobulin prophylaxis

	No gammaglobulin	Intravenous gammaglobulin infusions[a]		
		×2/week	×1/week	×1/2 weeks
No. of children	21	7	9	4
Patient years	14.7	4.7	3.5	1.5
Sepsis	2.7 (39)[b]	1.9 (9)	2.6 (9)	4.0 (6)
Suspected sepsis	2.0 (30)	3.2 (15)	4.0 (14)	2.0 (3)
Focal bacterial infection	2.0 (30)	3.0 (15)	0.6 (2)	2.7 (4)
Viral infection	2.1 (31)	2.8 (52)	1.1 (4)	5.4 (8)
Superficial yeast infection	0.8 (12)	0.4 (2)	0.6 (2)	–
Total	9.8 (144)	11.0 (52)	8.9 (31)	14.1 (21)

[a] The usual dose was 1 g of immunoglobulin per infusion except in 2 children who received 0.5 g. One child was first given 0.5 g and later 1 g. The infusions were given once or twice a week or in a few children once every 2 weeks
[b] Infection episodes per patient year (no. of episodes)

Discussion

The results show that septic infections are a major problem in nephrotic infants. The CNF children suffered from an average of 5 verified or suspected septic episodes per year.

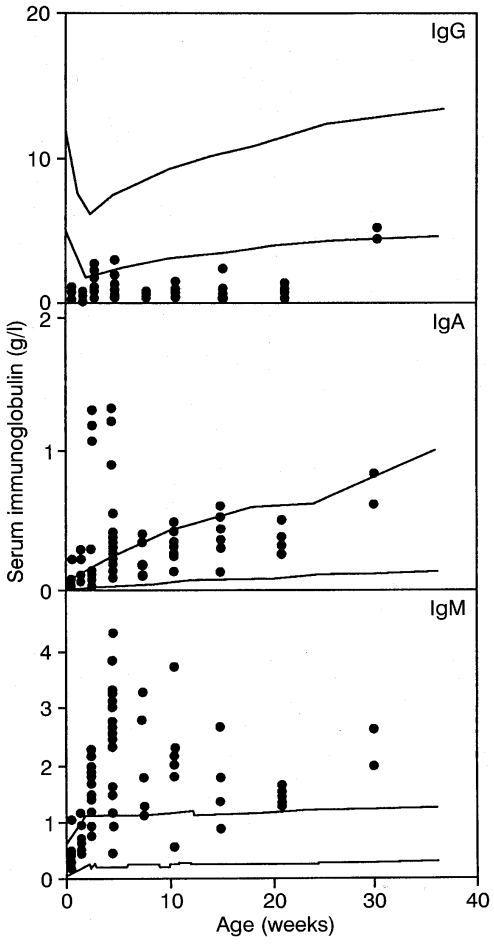

Fig. 1. Serum immunoglobulin levels during nephrosis in infants with congenital nephrotic syndrome of the Finnish type. IgG, IgA, and IgG levels were measured in 12 infants from 35, 51, and 65 samples, respectively. The *lines* indicate the normal area for the age

Our results confirm the previous observations that nephrotic children suffer from severe bacterial infections. In the report from Minnesota, 67 invasive bacterial infections occurred in 41 nephrotic children, including pneumonia (27 episodes), sepsis (13), peritonitis (15), urinary tract infection (10), and meningitis (2) [6]. Similarly, 23 of 75 CNF children died of infection in 1965–1973 in Finland. The cause of death was sepsis (6), pneumonia (6), peritonitis (4), meningitis (2), and some other infection (5) [7]. Compared with these two older reports, our children had less focal invasive bacterial infections and more septicemias.

Due to the heavy proteinuria, children with CNF need intravenous albumin infusions every night. Although these children are managed by experienced personnel, the infusions and other invasive procedures render these children susceptible to bacteremias. The etiology of the verified septic episodes also speaks for this: 40% of bacteremias were caused by coagulase-negative staphylococci which were mostly methicillin resistant. These represent the hospital strains colonizing the skin of patients and nursing personnel.

Children with congenital nephrosis need a permanent intravenous line, and we have used two kinds of central venous catheters, the tunnelled Hickman-Broviac catheter and the totally implanted venous access chamber system (Chemoport). The use of these catheters seems to increase slightly but not significantly the bacteremia rate compared with peripheral lines. No difference in this respect was found in the two catheter types. This is interesting since in children with cancer totally implanted chambers have shown a lower infection rate than catheters of Hickman-Broviac type [12]. The great majority of episodes were treated without catheter removal. In infants with repeated bacteremias the catheters were always changed.

Nephrotic children lose serum IgG antibodies into urine which impairs humoral immunity and increases the risk for bacterial infections. In particular, pneumococci and other bacteria with capsules are reported to cause infections in nephrotic children [10]. Our infants had very low levels of serum IgG antibodies, but the rate of infections caused by such bacteria was not high: 9% of the verified bacteremias were caused by pneumococci and none by haemophilus or

menigococci. It is possible that the elevated serum IgM levels, as well as the normal IgA levels, compensate for the deficiency caused by the urinary IgG loss. This is also favored by the fact that the mean rate of focal bacterial infections, such as middle ear infections, was only 2–3 episodes per year, which is normal for Finnish infants [13].

Because of the low serum IgG levels in CNF infants, some centers in our country had the habit of giving intravenous immunoglobulin to these patients either prophylactically or during septic episodes. The amount of IgG per infusion averaged 1 g, which is about 100–300 mg/kg. The prophylactic use of immunoglobulin did not affect the rate of septic or other infections. The natural explanation of this is that the infused IgG is rapidly lost into the urine. In 3 of our children the half-life of serum IgG was only 7–22 h, and all the infused IgG was lost in the urine within 2 days (data not shown). This has also previously been shown in three other infants with congenital nephrosis [14, 15]. To be effective, large amounts (500 mg/kg) of immunoglobulin should be given once in 2–3 days, which is costly and still would not protect against staphylococci and many other pathogens.

Penicillin- and co-trimoxazole-based antibiotic prophylactic treatments were given to 11 infants for a total of 11 patient years, but no significant protective effect was seen in the overall infection rate compared with infants not receiving any prophylaxis. The etiology of septic episodes differed, since all six pneumococcal bacteremias occurred in infants not receiving antibiotics. Since the majority of septic episodes were caused by hospital strains of Gram-positive and Gram-negative bacteria, a broad-spectrum antibiotic also covering the multiresistant staphylococci is needed for prophylaxis. This would be impractical and at the moment no prophylaxis is used in our patients.

Infants with CNF did not suffer from opportunistic infections caused by fungi, protozoa, or herpes viruses. The rate of viral respiratory tract and gastrointestinal infections was also low. With the exception of two episodes of candidemia, no invasive fungal infections were recorded. These findings fit with our observations that the cell-mediated immunity in these children is normal (unpublished results).

In conclusion, infants with CNF have a high incidence of septic episodes during the nephrotic stage. The symptoms are often vague and coincide with signs of focal infections occurring at the same time. Thus, a high index of suspicion is needed. Antibiotic therapy should be started promptly and should cover the major hospital strains of bacteria.

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