Abdominal complications in black and Indian children with nephrotic syndrome

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Abstract **Abdominal complications were detected and investigated in 19 (10%) of 191 children with nephrotic syndrome who experienced 35 episodes of these complications. Fourteen children were Indian with steroid-responsive nephrotic syndrome, and 5 were black, of whom 4 had membranous nephropathy and 1 focal proliferative nephritis. All had clinical features of peritonitis and hypovolaemia was frequently present. Eleven of the 35 episodes were culture-proven peritonitis (5 due to *Pneumococcus*, 6 due to Gram-negative bacteria) and in 24 the cultures were negative. Hypovolaemia occurred in 6 of the former group and 5 of the latter. The occurrence of these episodes bore no temporal relationship to steroid and cyclophosphamide treatment. Sixty-nine per cent of the complications appeared within the first 3 years of onset of the nephrotic syndrome and 8 of 19 patients experienced multiple episodes.**

In this study, hypovolaemia always occurred in the context of clinically detected peritonitis and not as a separate complication, suggesting infection together with fluid and protein losses as likely pathogenetic mechanisms.

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The prognosis of minimal change nephrotic syndrome, which accounts for the majority of childhood cases, is excellent, with nearly all patients (> 95%) surviving into adulthood.[1] The principal causes of death, for this and other histological categories of the nephrotic syndrome, are infection, hypovolaemia and thrombotic complications.[1] The survival rate of nephrotic children was only 33% in the 1940s and it has been stated that penicillin has done more for the survival of patients with the nephrotic syndrome than corticosteroids.[1] The main site of serious infection is the peritoneum, and the pneumococcus[2] and Gram-negative bacteria [3-5] are the dominant organisms. Infection usually occurs in the absence of a demonstrable intra-abdominal source of infection (primary peritonitis). The diagnosis is made on the basis of clinical signs of peritonitis together with signs of an exudate or positive bacterial culture from the peritoneal fluid, although the latter may often be negative. Further moderate to severe hypovolaemia[6-9] in the nephrotic syndrome may appear with similar abdominal signs and symptoms; therefore the differentiation of peritonitis from hypovolaemia may not be clear clinically. The likelihood that the pneumococcus is no longer the most frequent cause of primary peritonitis has been the subject of recent papers on this topic.[3-5] Most of the studies have focused on the richer industrialised countries and have included very little information from the Third World, especially Africa, where the nephrotic syndrome is different in many respects.[10]

For these reasons we have reviewed our experience with abdominal complications, concentrating on episodes of peritonitis and hypovolaemia in South African black and Indian children with nephrotic syndrome. We present our findings below.

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Patients and methods

We reviewed the clinical and laboratory data on 191 children with the nephrotic syndrome who had been seen at the Paediatric Unit of King Edward VIII Hospital, Durban, between 1981 and 1988. There were 19 children in whom 35 episodes of abdominal complications (as defined below) with fever occurred. Pneumococcal vaccine had been given to 12 of these patients. The 7 remaining patients were subsequently immunised. All children underwent a thorough clinical examination and a special note was made of previous and current therapy.

The terms used in the text are defined as follows:

1. **Nephrotic syndrome** — heavy proteinuria (> 2 g/m²/d), hypo-albuminaemia (< 30 g/l) and oedema.

2. **Steroid-responsive nephrotic syndrome** — this included all Indian children who had biopsy-proven minimal change (and who in this study were always responsive to steroids) and others who were responsive to steroids but were not biopsied and were presumed to have minimal change.

3. **Relapse** is the recurrence of heavy proteinuria. In the children described here this was always accompanied by hypo-albuminaemia and oedema.

4. **Abdominal complications** — (*i*) peritonitis: clinical signs of peritoneal irritation (i.e. abdominal pain, tenderness); more serious cases had guarding and/or rigidity with a raised total white blood cell count and/or a neutrophilic leucocytosis. These features were often accompanied by hypovolaemia; (*ii*) hypovolaemia: the presence of hypotension, poor volume pulses, pallor and cold limbs; (*iii*) other complications such as severe diarrhoea and/or vomiting and dysentery were included in the study. Surgical complications, namely acute appendicitis, bowel obstruction and perforation were excluded clinically and radiologically. Acute appendicitis, bowel obstruction and/or perforation were not detected in any patient.

5. **Remission** — the absence of proteinuria, oedema and a normal serum albumin value.

Investigations

Seventy-three per cent of Indian children have minimal change nephrotic syndrome[10] and were therefore biopsied only if they were steroid-unresponsive or had any other unusual features. All black children were biopsied. On presentation, all the children had blood, urine and, where possible, peritoneal cultures taken. These were collected and processed in a standard manner. Stools were examined microscopically and cultured if diarrhoea were present. Full blood count, blood urea, serum creatinine and electrolyte estimations were performed and chest radiographs taken.

Management

Penicillin and an aminoglycoside were administered intravenously once the investigations had been undertaken. Antibiotics were discontinued when the temperature and white cell count were normal and the abdominal signs had settled. The minimum period of antibiotic treatment was 5 days. Some patients required 7 - 10 days of treatment. Where indicated volume support was given as albumin or plasma and severe oedema was treated with salt-free 20% albumin followed by intravenous furosemide. Maintenance diuretics such as thiazide, triamterene and aldactone were used. Patients were not fed orally until the abdominal signs were settling. This usually happened within 12 - 24 hours; occasionally it took up to 48 hours. Diet comprised low-salt fluid and food, and a protein intake of 3 - 4 g/kg/d.

Results

Clinical characteristics of abdominal complications

Table I lists the race groups, histological categories, ages and sexes of the 19 children. The dominance of boys, steroid sensitivity in Indians, membranous and proliferative changes in blacks and the age distribution are all fairly typical of the disease in Durban. The major clinical features, investigations, relationship to therapy and interval from first diagnosis of nephrotic syndrome to case of peritonitis are shown in Table II. Proteinuria and varying degrees of oedema were found at presentation in all cases. In 10 cases the oedema was severe. Fever, abdominal pain and tenderness occurred in all of them. Guarding and rigidity appeared to be more severe in the culture-positive cases. There were 11 positive blood cultures. Of the 11 episodes where there was accompanying hypovolaemia, 6 were blood culture-positive. Twenty-four abdominal episodes had clinical signs of peritonitis but were culture-negative; 5 had accompanying hypovolaemia. Three of the 19 instances of culture-negative peritonitis without hypovolaemia were accompanied by upper and lower respiratory infections; chest radiographs confirmed pneumonia in 2 children.

Three patients developed pneumococcal peritonitis following immunisation against pneumococcus. One child with pneumococcal peritonitis had pneumococcal meningitis as well. In 21 of these episodes volume support was necessary; 11 of these were hypovolaemic and a further 10 associated with severe oedema.

The number of abdominal episodes per patient is indicated in Table III. None of the episodes could be attributed to surgical complications.

Bacteriological cultures

The organisms cultured in the 11 instances of peritonitis were as follows: 5 pneumococci, 2 *Escherichia coli*, 2 *Klebsiella pneumoniae* and 2 *Haemophilus influenza* type B. Two children had more than 1 episode each, 1 had *E. coli* and *pneumococcus*, the other *E. coli*, *K. pneumoniae* and *H. influenza* type B. In 3 instances cultures were positive from both blood and peritoneal fluid, in 1 instance the peritoneal culture only was positive, and the remaining 7 cases were blood-culture positive. A further 5 peritoneal cultures were negative. All urine cultures were negative.

TABLE I.
Patient data

	Indian	Black
No.	14	5
Boys	10	5
Girls	4	–
Category of nephrotic syndrome	14 minimal change (2 biopsy proven)	4 membranous, 1 focal proliferative
Age range (yrs)	2 - 9	4 - 9

TABLE II.
Comparison of key features in the 35 episodes of abdominal pain

	Total	Peritonitis: Culture-positive (11)	Peritonitis: Culture-negative (24)
Clinical features			
Fever	35	11	24
Abdominal pain	35	11	24
Tenderness	35	11	24
Guarding	15	9	6
Rigidity	17	10	7
Proteinuria	35	11	24
Severe oedema	10	5	5
Hypovolaemia	11	6	5
Vomiting	9	4	5
Diarrhoea	3	1	2
Blood results			
Haemoglobin (g/dl)		11,81 ± 1,46	11,67 ± 1,61
White cell count (X 10^9/l)		12,10 ± 5,8	16,3 ± 10,0
Serum albumin (g/l)	35	13,4 ± 6,9	11,75 ± 2,89
Low serum sodium	2	0	0
High blood urea	4	2	2
Relationship to therapy*			
No therapy	7	0	7
Interval between therapy and episodes (mo.)			
0	6	0	6
< 3	7	4	3
4 - 6	2	0	2
> 6	13	3	10
Interval between diagnosis of nephrotic syndrome and abdominal episode (mo.)		46,0 ± 43,6	35,16 ± 37,43

* Steroid or cyclophosphamide.

TABLE III.
Number of abdominal episodes experienced by individual patients

	Episodes per patient		
Patients	No.	CP	CN
10	1	1	9
5	2	4	6
1	4	3	1
1	5		5
1	6	3	3

*CP = culture-positive; CN = culture-negative.

Investigations (Table II)

The haemoglobin value was similar in all groups; the white cell count was higher in episodes of culture-negative peritonitis with hypovolaemia. All the episodes were associated with hypoproteinaemia. Four children had raised blood urea levels ranging between 10,3 and 17,3 mmol/l with their serum creatinine values in the normal range; this was suggestive of renal hypoperfusion. In two

hypovolaemic episodes (occurring in the same patient) the serum sodium was 117 mmol/l and 120 mmol/l. In the former episode, the low serum sodium level was related to diuretic therapy. In the latter episode, associated with bloody diarrhoea, the stool microscopy revealed *Entamoeba histolytica.*

Time interval from diagnosis of nephrotic syndrome to peritonitis and hypovolaemia

The interval from first diagnosis of nephrotic syndrome to the occurrence of the episode of peritonitis and hypovolaemia varied from 0 to 116 months with a mean of 40,5 months. The time intervals for each sub-category are given in Table II. There was no significant difference in the time intervals between the two groups. Twenty-four cases of peritonitis (69%) occurred within the first 3 years of the disease; 1 patient had 5 bouts over 10 months, another 6 over 42 months.

Relationship of peritonitis to steroid and cyclophosphamide treatment (Table II)

None of the 5 black children was on steroid or cyclophosphamide at the time they had peritonitis. Details of steroid and/or cyclophosphamide therapy in relation to the first episode in the 14 Indian children is given in the table. Thirteen of 28 episodes occurred more than 6 months after treatment had ceased. All the children had proteinuria and oedema at the time of presentation.

Response to antimicrobial therapy

Most cases of culture-negative peritonitis responded rapidly (within 2 days) to antibiotic therapy; those with Gram-negative infections improved more slowly, settling within 3 - 6 days. One child with pneumococcal meningitis recovered in 7 days. The 3 cases of respiratory infections (2 pneumonias, 1 upper respiratory tract) settled in 3 - 6 days and the amoebiasis settled in 5 days.

Deaths

No deaths occurred during the episodes of hypovolaemia and/or peritonitis. One black child with focal proliferative nephritis died 4 months after the episode of suspected peritonitis. She had severe oedema, proteinuria and renal failure.

Discussion

Two well-described and equally serious complications of the nephrotic syndrome are primary peritonitis[3-5] and, less frequently, hypovolaemia.[6,7] These two complications may overlap.[7,8] In a description by Egan[8] of 4 patients developing shock in the nephrotic syndrome, 1 patient had septicaemia. The nephrotic crisis described by Farr and Macfayden[7] was characterised by the sudden onset of abdominal pain, fever and shock sometimes associated with infection. The main pathogenic factor implicated in their study was hypovolaemia following massive proteinuria.[7] Abdominal pain, tenderness, vomiting and diarrhoea without fever occur in the nephrotic child with generalised oedema and probably reflect oedema of the intestinal wall and pooling of fluid in the mesenteric plexus.[11] In the nephrotic syndrome, hypovolaemia associated with sepsis is not only caused by fluid and protein losses (in urine, stools and interstitial space) but also by a decrease in systemic vascular resistance. This possibility is supported by the fact that in this study hypovolaemia was often associated with severe oedema (when there is fluid and albumin loss from blood vessels to interstitium) and that hypovolaemia was detected more frequently in those with culture-positive peritonitis. Hypovolaemia did not mask the diagnostic clinical signs of peritonitis. However, in the presence of ascites, tenderness and guarding were present but rigidity less so. The serious signs of peritonitis, guarding and rigidity were present in nearly every episode which was culture-positive.

Gram-negative organisms were cultured in 55% of the positive blood cultures. These organisms have been reported in a number of recent studies as causal agents of primary peritonitis.[3-5] In all patients with Gram-negative infections, radiological examination excluded bowel perforation, supporting a haematogenous aetiology for these infections. The pneumococcus was cultured in the remainder. Primary peritonitis is generally commoner in girls. The nephrotic syndrome is commoner in boys and in the context of this study, primary peritonitis occurred more often in boys.

Pneumococcal peritonitis in the nephrotic syndrome is generally accepted to be of haematogenous origin. The predisposition to infection with pneumococcus and Gram-negative organisms in children with nephrotic syndrome is not well understood. Studies have shown a variety of immunodeficiencies associated with the syndrome. These provide some understanding of the immunopathology predisposing to infection.[12-16] A satisfactory serological response to the polyvalent pneumococcal vaccine protects children from developing peritonitis of the pneumococcal types in the vaccine.[17] This is the basis for the routine administration of pneumococcal vaccine in these children.

Most episodes of peritonitis and hypovolaemia occurred within the first 3 years of the onset of nephrotic syndrome; one occurred 9½ years after the onset of the disease. The episodes were not specifically related to treatment or relapse. Patients presented during or following completion of steroid or immunosuppressive treatment, others during relapse, while some children had been in remission for variable periods of time. A few children appeared to develop peritonitis and hypovolaemia more readily than others. Eight of the 19 children had a total of 17 bouts and 1 patient had as many as 6. Recurrent bouts in an individual child and their occurrence during a period of remission are unusual but understandable given the persistence of immunological abnormalities during remission in children with nephrotic syndrome.[12] Although a range of immunodeficiencies has been extensively documented in childhood nephrotic syndrome,[12-16] the gratifying response to treatment and recovery in all instances suggests that immune deviations are subtle and probably mild. The fact that fever was associated with the onset of all instances of peritonitis suggests, but does not prove, that occult infection was the likely triggering event for the development of these episodes.

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