Management of Nephrotic Syndrome in Children: A Review

Pages with reference to book, From 113 To 116

Mushtaq A. Khan (Children's Hospital. Pakistan Institute of Medical Sciences, Islamabad.)
Tabish Hazir (Children's Hospital, Pakistan Institute of Medical Sciences, Islarnabad.)

Introduction

The term nepkrotic syndrome (NS) refers to the presence in a patient of proteinuna, hypoproteinemia, edema and hyperlipidemia. It is the second most common primary renal parenchymal disease in children aged 15 years or less[1]. It appears to be more common in Asian children, with a prevalence of 9-16 per 100,000 as compared to Caucasian children of 4 per 100,000[2].

Nephrotic syndrome in children differs from that in adults due to the reason that about 80% of cases have primary nephiotic syndrome with minimal change histopathology dominating. Minimal change nephrotic syndrome (MCNS) has a good correlation with steroid responsiveness thereby, giving childhood NS a more favourable prognosis as compared to adults. However, despite a good initial response to steroids, most cases of nephrotic syndrome relapse. These relapses tend to be quite common and may be very frequent in a sizeable proportion of nephrotic children[3]. There is increasing evidence to suggest that the tendency to relapse is influenced by the duration of treatment of the initial episode[4-6]. Nephrotics with minimal changed histopathology, who frequently relapse or become steroid dependent continue to pose a therapeutic dilemma to the treating clinician, as there is no satisfactory steroid regimen at present that can decrease the tendency to multiple relapses without resulting in some degree of steroid toxicity[7]. The problem is further complicated by the lack of uniformity in making a decision to refer the patient to a paediatric nephrologist to perform a renal biopsy, to sswitchover to cytotoxic immunosuppressive drugs and to decide about the duration of such a therapy (Table I).

Table I. Indications for referral to a pediatric nephrologist.

1. At the outset if the age is less than 1 year or older than 12 years as minimal change disease is less likely and the underlying pathology is to be more clearly defined.
2. If the child has atypical features with a mixed nephritic/nephrotic picture associated with gross hematuria, renal insufficiency, hypertension or hypocomplementemia.
3. During the course of treatment with steroids, if complication ensue such as acute renal failure, thrombosis etc.
4. All steroid resistant nephrotics.
5. Development of steroid resistance in previously steroid sensitive nephrotic.
6. Before starting cytotoxic drugs.
7. Steroid toxicity.

There is very little uniformity in the management of nephrotic children in our community. The duration and dosage of steroids for the treatment of initial episode continues to be inadequate. The management of relapses tends to be even more erratic. The referral to the tertiaiy care hospitals is random resulting in wastage of lot of time and resources. The current practice of managing nephrotic syndrome in the community need to be streamlined. There is a need to develop guidelines for general practitioners and paediatricians working in the community wko constitute the first encounter with nephrotic children in a vast majority of cases. It is imperative that great importance be given to the proper management of initial episode of nephrotic syndrome. The dosage and duration of steroid therapy is to be clearly specified. Information on the proper management of relapses should be disseminated. There is a need to create awareness about features which suggest a diagnosis other than a minimal change disease so that a timely referral is made to a tertiary centre having the facility to perform a renal biopsy (Table II).

Table II. Indications for renal biopsy .

At onset	
1.	features suggestive of a diagnosis other than MCNS
2.	presentation before 1st year or after 6 years of age.
Intermediate	
	failure to respond after 28 days of steroid therapy.
Late	
1.	frequent relapsers
2.	steroid dependence
3.	development of steroid resistance
4.	change in the clinical course
5.	prior to beginning treatment with a course of cytotoxic drugs.

In an attempt to achieve this objective a comprehensive review of literature was done to develop such guidelines which will help to streamline the management of nephrotic syndrome in our community with the aim to: 1) induce remission, 2) prevent relapses, 3) properly treat relapses, 4) avoid side effects of therapy.

Classification

The classification of nephmtic syndrome into congenital, primary and secondary nephrotic syndrome is fraught with paradoxes. A spectrum of renal histological findings have been described in patients with primary nephrotic syndrome having unpredictable response to steroids. Some childrenwith MCNS do not respond to steroids while many with focal segmental glomeruloselerosis (FSGS) do[8]. Such exceptions raise the problems of both classification and terminology. The British Association for paediatric nephrology classifies nephrotic syndrome as either steroid sensitive (SSNS) or steroid resistant nephrotic syndrome (SRNS), irrespective of the underlying histopathology. Such classification not only seems more pragmatic but is also more predictive of the prognosis since steroid resistant nephrotic syndrome consists of rare disorders with varying response to treatment and therefore, carries a poorer prognosis[9]. Since histopathology in most children with primary nephrotic syndrome is not determined, it seems more appropriate that they are classified according to their response to steroids.

Clinical features

The usual presenting manifestation of nephrotic syndrome is edema developing over several weeks. Initially periorbital, the edema becomes generalized with ascites and pleural effusion. There is oftenapreceding history of an upper respiratory tract infection which often precipitates relapses. Despite gross edema, the patient usually does not appear seriously ill. There may be oliguria due to 'hypovolaemia, which also predisposes to thrombosis. Hypertension may be present in 10-15% of cases[10]. Microscopic haematuna has been reported in 23% of MCNS and 78% of FSGS patients in ISKDC series[11]. The clinical features which suggest a diagnosis other than MCNS are summarized in Table III.

Table III. Features suggestive of a diagnosis other than MCNS.

Clinical features.	
1.	Age <1 years or >6 years
2.	Haematuria, Hypertension
3.	Features suggestive of a collagen vascular disorder
4.	Past history suggestive of "Nephritis".
5.	Family history of end-stage renal disease
Laboratory features	
1.	Decreased renal functions
2.	Haematuria
3.	Non-selective proteinuria
4.	Decreased C_3, C_4
5.	Only mild hypoalbuminemia
5.	Mild hypercholesterolemia

Investigations

Urinalysis

Most nephrotics will have marked proteinuria which on an albustix will characteristically reads 3+ or 4+. Albustix are cheap, reliable and give instant results. However, this test has sensitivity of only 70% and specificity of only 68% when compared with 24 hour quantification of urinary protein[12]. However, 24 hour quantification has the drawback of inherent time delay, is subject to collection errors and is difficult to obtain in an out-patient setting[13]. Estimation of protein/creatmine ratio in an early morning urine (EMU) is an acceptable alternative of measuring urine protein excretion without a 24 hour urine collection. The upper limit for normal EMTJ protein/creatinine ratio is 200 mg/mmol[14].

Blood studies

Total serum proteins in nephrotics is characteristically reduced to between 4.5 and 5.5 Gm/dl. Senim albumin concentration usually falls to below 2 Gm/dl[15]. Hyperlipidemia comprises part of definition of the nephrotic syndrome. Serum cholesterol is usually elevated to above 400 mg/cit and total lipids are commonly increased to values as high as 4.5 g/dl[16]. In selected cases, C3 and C4 components of complement, antistreptolysin 0 titre and antinuclear factor should also be measured.

Management

In our setup it is advisable to admit the child to the hospital with the first episode for making a proper diagnosis and monitoring the therapeutic response. This time should also be utilized for educating the caretakers about the disease and teaching them simple procedures like checking the urinary proteins with albustix by proper colour matching.

Since MCNS accounts for 80% of nephrotic children and has a more or less good response to steroids an initial trial of steroids without doing a renal biopsy is a standard recommendation, provided the patient does not have any features suggestive of forms other than MCNS (Table III).

Predmsolone is the standard steroid for therapeutic management of nephrotic syndrome. It is started in the initial dose of 60 mg/M sq/day or its equivalent 2 mg/kg according to the body weight. Once urinary protein is 0-trace with albustix on three consecutive days, the remission is considered to have been achieved[17]. The dose of predmsolone should then be reduced to 40 mgfM sqon alternate days for a period of upto three months. The steroids can then be discontinued abruptly without tapering since alternate day regimen does not cause suppression of pituitary- adrenal axis. The steroid side effects tend to be less in patients who are on alternate day as compared to daily regimen[18,19]. Moreover, this regimen decreases the likelihood of relapses which is higher when shorter period regimens are employed[20].

The children who do not go into remission by the end of four weeks are considered to be steroid resistant. A renal biopsy is indicated at this stage to determine the underlying histopathology. Such children should be referred to a paediatric nephrologist.

Relapses

Table IV. Definitions. Derived from international study of kidney disease in children. (ISKDC).

Relapse: Urinary proteins ++ or more with albustix on 3 consecutive days.
Frequent relapses: Two or more relapses within six months of initial response or four or more relapses within any 12 month period.
Steroid Dependence: Two consecutive relapses occurring during corticosteroid treatment or within 14 days after its cessation.
Steroid Resistance: Failure to achieve response in spite of 4 weeks of treatment with prednisolone (60 mg/M sq/day).
Remission: Urinary protein=0/trace on albustix on three consecutive days.

Relapses (Table IV) are a conunon feature of childhood nepluotic syndmme. Seventy-five percent of nephrotic children will have relapse of the disease. Out of these 25-30% of children have infrequent relapses and usually respond well to further courses of steroids. The remaining patients have either frequently relapsing or stemid dependent nephrotic syndrome[21].

Upto 20% of the relapses will remit spontaneously[22]. Therefore it is advisable to defer treatment upto five days provided the child is not allowed to become edematous.
The regimen for first two relapses is identical to that of initial episode. Prednisolone 60 mgfMsq/day is given until remission is achieved followed by 40 mg/Msq on alternate days for 3 months[23].

Frequent Relapses

A child with two or more relapses within six months of initial response or four or more relapse within any twelve months period is classified as frequent relapser. At this time, there is no standard approach to evaluation and management of children with frequently relapsing, corticosteroid dependent NS. Some physicians rely on their clinical awareness whereas others depend on the histopathologic findings. However, most authorities recommend low dose long term maintenance, prednisolone for frequent relapses. The dose should be sufficient to maintain remission but as low as possible in order to minimize side effects. The recommended dosage is 0.1-0.5 mg/kg by weight on alternate days for a minimum of 3-6 months[24].
If the child relapses while still being on low dose maintenance stemids or develops unacceptable side effects or toxicity due to the drug then alternative treatment has to be considered. The decision to use alkylating agents such as eyelophosphanilde with its serious side effects and potential toxicity must be balanced against the risks of continued high dose steroids or an inadequately controlled nephrotic state. It is important to discuss indetail withthe parents the advantages and disadvantages of such therapy before its institution. Most centres obtain satisfactozy results with a dosage of 2 mg/kg/day given for no more than 90 days. Cyclophosphamide in conjunction with steroids is preferred[21]. It has been observed that upto 65% of patients remain in remission for atleast 5 years after this treatment. Permanent remissions have been reported in upto 50% of cases[22]. Alternatively, chiorambucil in a dose of 0.2-0.3 mg/kg/day alongwith steroids can be used fora period of 10-12 weeks[23].
Levamisole is an immunostimulant. Due to its steroid sparing effect and few side effects it can be used in frequent relapsers who are dependent on high dose prednisolone. It is used in a dosage of 2.5 mg/kg twice a week[24].
Cyclosponn should usually be reserved for cases that continue to be steroid dependent despite a course of cyclophosphamide.In special situations, such as boys approaching puberty, it is now being increasingly employed in preference to cyclophosphamide which carries a probability of testicular damage in pubertal boys[25,26]. Such therapy has to be carried out under the close supervision of a paediatnic nephrologist and all such cases must be referred.
High dose pulses of intravenous methylprednisolone have been utilized in a small series of patients and appear to decrease the frequency of relapses[27].

Steroid toxicity

The side effects of long-term steroid therapy are numerous and can be serious. The physician must carefully explain to the parents the hazards of steroid therapy. All intercurrent illnesses must be appropriately treated. In addition, a careful and regular monitoring of various side effects is essential. All such children should be followed up eveiy three months for their blood pressure and growth measurements and their eyes should be checked for possible development of cataracts on yearly basis[28]. In case of growth retardation, further evaluation must be done and a decision to switch over to alternate therapy with cytotoxic drugs be considered.

Supportive treatment

Supportive management should be focussed onalleviating the edema until remission is achieved in steroid responsive patients. Child should be actively mobile with a balanced, no added salt diet adequate in energy and protein. Excessive fluid intake should be avoided.
Diuretics should be used judiciously. Thiazides are effective by mouth and can be given at home. Hydrochlorthiazide may be given in a dosage of 2-5 mg/kg/day in two divided doses.Potassium

supplementation should be given alongwith thiazides to prevent potassium depletion. Frusemide in a dose of 1-2 mg/kg/day can be given in combination with spironolactqne (2 mg/kg/day)[29].
Blood pressure should be monitored. If it exceeds normal limits for age and sex, then short-term treatment with antihypertensives is instituted. Atenolol in a dose of 0.5-1 mg/kg/day or Nifedipine inadose of 0.25-2 mg/kg/day canbe employed[30].
Nephrotics are usually prone to infections withencapsulated organisms specially streptococcus pneumonia[32]. In the presence of gross edema it is a pragmatic practice to use oral penicillin 125 mg or 250 mg twice daily until the edematous state has resolved. Any focus of obvious infection should be treated properly.
Use of salt poor albumin infusions is expensive and its effect is transient since the albumin rapidly leaks out in the urine. It should be reserved for situations where there is gross edema which is resistant to diuretics. Salt poor albumin alongwith intravenous frusemide may be very helpful in producing diuresis and alleviating the distress in a grossly edematous child or in a situation where there is rapid loss of proteins leading to hypovolemia. Salt poor albumin should be given in a dose of 0.5- 1.0 gm/kg upto 25 gm over a period of 30 to 60 minutes followed by 1-2 mg/kg of frusemide intravenously[32].

References

1. H. William Shnaper, Alan M. Robson. Nephrotic syndrome: minimal change disease, focal glomerulosclerosis and related disorders in Robert W. Schrier, Carl, W. Gottscchalk (eds.) Diseases of the Kidney. 4th ed. Vol. II, Boston/Toronto, Little Brown and Co., 1988, pp. 1949-87.
2. Sharpes, P.M., Poulton, J. and White, R.H.R. Steroid responsive nephrotic syndrome is more common in Asians. Arch. Dis. Child.. 1985;60: 1014-7.
3. Lewis, MA., Baildon, E.M.,Davis, N.etsl. Nephrotic syndrome: From toddlers to twenties. Lancet, 1989;i:255-9.
4. Chonara, IA. ,Henry, D. and Meadow, SR. Low dose prednisone in nephrotic syndrome, Arch. Dis. Child., 1989;64:610-2.
5. Bordehl, J. Conventional therapy for idiopathic nephrotic syndrome. Clin. Nephrol., 1999:1;35 (suppl):58-15.
6. Rees, L., Greene, S.A., Jones, J. et at. Growth and endocrine function in steroid sensitive ncphrotic syndrome. Arch. Dis. Child., 1988;63 :79-85.
7. Waldhera, R., Gubtey, M.C., Levy, M. et at. The significance of pure diffuse mesangial proliferation in idiopathic nephrotic syndrome. Clin. Nephrol., 1978;10:171-3.
8. Bergstien, j.M. Nephrologic diseases. In Behrman (ed.) Nelson textbook of paediatrics. l4thed., Philadelphia, W.B. Saunders & Co., 1992, p. 1342.
9. International study ofkidney disease in children. Early identification offrequent relapsers among children with minimal change nephrotic syndrome. J. Psediatr., 1982;101 :514-518.
10. Abitol, C., Zillerueolo, G., Freundlich, M. et al. Quantification of proteinuria with urinary protein/creatinine ratios and random testing with dipstieks in nephrotic children. J..Paediatr., 1990;116:243-247..
11. Robson, W.L.M. and Leung, A.K.C. Clinical evaluation of children with proteinuria Contemp. Paediatr., 1991 ;2:17-24.
12. Eliaes, J.S., Grifliths, PD., Hocking, M.D. et at. Simplified quantification of urinary protein excretion in children. Clin. Nephrol., 1988;30:225-9.
13. Bamett, H.L., Schoeneman, M., Bernstein, J. et al. The nephrotic syndrome. In Edelman CM. (ed.) Paediatric kidney diseases. Boston, Little, Brown, 1978, p. 695.
14. Habib, R. and Kleinknechi, C. The primary nephrotie syndrome of childhood: Classification and clinieopathological study of 406 cases. Psthol. Annu., 1971;6:417-20.

15. MeEnety, PT. and Strife, CF. Nephrotic syndrome in childhood management and treatment in patients with minimal change disease, Mesangial proliferation, or focal glomeruloscherosis. Pediatr. Clin. North Am., 1982;29:875-87.
16. Shnaper, H.W. and Robson, AM. NephrOtic syndrome: Minimal change disease, focal glomerulosclerosis and related disorders in Robert W. Schrier, Carl, W. Gottschalk (eds) Diseases of the Kidney. 4th Ed. Vol.11 Boston/Toronto, Little Brown and Co. 1988, p. 1964.
17. Brodehl, J., Krohn, H.P and Ehrich, J.H. The treatment of minimal change nephrotic syndrome: Cooperative studies of the arbeitagemeinsehaft fur paediatrische nephrol (APN). KIm. Paediatr., 1982;1 94:162-5.
18. Grupe, WE. Primary nephrotic syndrome in childhood. Acts. Pediatr, 1979;26:163-207.
19. Wingen, A.M., Muller, Wiefel, O.E., Secharer, K. Spontaneous remission in frequently relapsing and steroid dependent idiopathic nephrotic syndrome. Clin. Nephrol., 1985;23:35-8.
20. International study of kidney diaeaae in children. Nephrotic syndrome in children. A randomized trial comparing two prednisolone regimens in steroid responsive patients who relapse early. J.Paediatr., 1979;95:239-43.
21. Robson, W.L.M. and Leung, A.K.C. Nephrotic syndrome in childhood. In Barneas, DeVivo, Morrow, Oski, Rudolph. (eda). Adv. Pediatr., 1993;40:31 2.
22. Barratt, TM. and Soothill, J.L. Controlled trial of cyclophosphamide in steroid sensitive relapsing nephrotic syndrome of childhood, Lancet, 1970;ii:479-82.
23. International study ofkidney diseases in children. Prospective controlled trial of cyclophosphamide in children with nephrotic syndrome. Lancet, 1 974;ii:423-7.
24. Grupe, W.E., Makker, S.P and Ingelfinger, JR. Chlorambueil treatment of frequently relapsing nephrotie syndrome. N. EngI. J. Med., 1976;295:746-9.
25. British association for pediatric nephrology. Levamisole for cortieosteroid dependent Nephrotic syndrome in childhood. Lancet, 1991 ;337: 1555-7.
26. Tanaka, R., Yoshikaeva, N., Kitsno, Y. et al. Long term cyclosporin treatment in children with steroid dependent nephrotic syndrome. Pediatr. Nephrol, I 993;7:249-52.
27. Webb, K.L., Sargent, P. and Burke, J.V. Cyclosporin therapy in steroid dependent nephrotic ayndrorne. J. Pediatric-Child Health. 1993;29: 181-91.
28. Ponticelli, C., lmbasciatin, E.,Case, N. et al. Intravenous methylprednisolone in minimal change nephrotic syndrome. Br. Med. J., 1980;280:68 5-686.
29. Brocklebank, J.T, Harcourt, R.B. and Meadow, S.R. Cortieoateroid induced, cataracts in idiopathic nephrotic syndrome. Arch. Dis. Child., 1982;53:30-1.
30. Nash, M.A., Edelmann, C.M., Bernstein, 5., Barnett, H.L. The nephrotic syndrome. In Chester U Edelmann Jr. (ed.) Pediatric Kidney Disesse. Vol. 2, Boston/Toronto, Little Brown Co., 1992, pp. 1247-63.
31. Report of a workshop by the British association for paediatric nephrology and research unit, Royal College of Physicians. Consensus statement on management and audit potential for steroid responsive nephrotic syndrome. Arch. Dis. Child., 1994;70:151-7.
32. Krensky, AM, Inglefinger, J.R. and Gruge, WE. Peritonitis in childhood nephrotic syndrome. Am.J. Dis. child., 1982;136:732-36.