Journal of Bangladesh College of Physicians and Surgeons
Vol. 22, No. 2, May 2004

Childhood Nephrotic Syndrome : Rational of Management

MGM UDDIN[a], MH RAHMAN[b], A BEGUM[c], MM HOSSAIN[d]

Summery:

We have analyzed the appropriateness of therapy of primary care physicians in 107 children with nephrotic syndrome referred to our institute from January 2001 to December 2003. Prednisolone was administered in adequate doses in 52 (54.73%), and for adequate duration in 40 children (42%). Adjunctive cyclophosphamide therapy was administered in the recommended doses in 72% of cases and duration in 34% of the cases. On evaluation of therapy it was observed that inappropriate treatment had been administered by 26% of the pediatricians, 72% of adult physicians and 81% of general practitioners. This study highlights the lacunae in the current state of knowledge amongst the primary physicians and highlights the need for creating greater awareness regarding the therapy of children with nephrotic syndrome.

(J Bangladesh Coll Phys Surg 2004; 22 : 57-60)

Introduction:

Nephrotic syndrome is an important chronic disorder in children. Minimal Change Disease (MCD) is the commonest histopathological variety[1]. This has an excellent response to steroids. Majority of the cases do not pose therapeutic problems and can easily be managed by the primary physicians if one adheres to the standard protocol[2]. Appropriate therapy helps in minimizing side effects. More over it has now been demonstrated that the adequacy of initial therapy effects the subsequent course of the illness[2,3]. The intensity of initial treatment may decrease the rate of subsequent relapses[4]. This study was done to see the appropriateness of therapy by primary physician in children with nephrotic syndrome in this country prior to their referral to tertiary care centres.

Materials and method:

The children with nephrotic syndrome referred to Bangabandhu Sheikh Mujib Medical University Hospital, Dhaka from the only public sector tertiary care center for paediatric nephrology January 2000 to December 2003 between one and 15 years of age. Children with systemic disease and congenital nephrotic syndrome has been excluded from the study. During this period 107 children with nephrotic syndrome were seen in this institute. The referring physicians comprised pediatricians, adult physicians and general practitioners. During initial evaluation apart from clinical exam detailed drug history was carried out to find out the appropriateness of therapy of the referring physicians, in terms of dose and the duration of prednisolone and cyclophosphamide. The currently recommended treatment protocol by the ISKDC for initial episode i.e. 2mg /kg (max 60mg) in two-three divided doses daily for 6 weeks, followed by 1.5mg / kg (max 40 mg), as a single morning dose on alternate day, for the next 6 weeks[9].

A relapse is treated with same drug in a dosage of 60mg/kg/m^2/ day till remission (documented for 3 days) followed by 40mg/m^2/alternate day x 4 weeks[3,5-8]. Cyclophosphamide administered in dose of 2mg/kg/day for 8 to 12 weeks in frequent relapsers and steroid dependent patients respectively was taken as standard for comparison[9]. Inappropriate therapy means any other regimen in terms of dose and duration beyond above mentioned protocols.

The name, address and qualifications of the referring physicians were duly recorded. Urine examination

a. Dr. Md. Golam Muin Uddin, Professor of Pediatric Nephrology, BSMMU, Dhaka

b. Dr. Md. Habibur Rahman, Associate Professor of Pediatric Nephrology, BSMMU, Dhaka

c. Dr. Afroza Begum, Associate Professor of Pediatric Nephrology, BSMMU, Dhaka

d. Dr. Md. Moazzam Hossain, Professor of Pediatric Nephrology, BSMMU, Dhaka

Address of Correspondence : Dr. Md. Golam Muinuddin, Professor, Pediatric Nephrology, BSMMU, Dhaka-1000, Bangladesh

and blood biochemical investigations were done in all the patients. The diagnosis of nephrotic syndrome was based on the standard ISKDC criteria[10].

Kidney biopsies were carried out if:

i) the age was less then one and more then 10 years;.

ii) there is no response to four weeks steroid therapy;

iii) there is unusual clinical features (sustained hypertension, gross haematuria) or there is hypcomplementemia, elevated blood urea and creatinine.

iv) there is persistent microscopic haematuria; and before starting treatment with cyclosporin A.

Based on their subsequent response to adequate steroid therapy, these patients were categorized as frequent relapsers (FR), Steroid dependent (SD), initial non- responders (INR) and subsequent non- responders using standard case definitions[6].

Results:

Of 107 children there were 70 boys, 37 girls. The age of onset of disease was 4.2 years (range 1- 15 years), and the mean age at referral was 5.6 years (1.2 - 15years). The duration of followup at the institute ranged from one to 20 months (mean 16±42 months). Of the 107 children, 103 (96%), had received steroids prior to referral while 23(21°l0) had also been treated with oral cyclophosphamide. Of these, accurate details of previous therapy regarding duration and doses were available in 95 children. The distribution of these children based on the adequacy of dose and duration of the previous steroid therapy is shown in Fig 1. Only 52 (54.73%) children had received steroids in appropriate doses and 40(42%) had received therapy for appropriate duration prior to the referral.

In contrast inadequate therapy in terms of dose and duration had been given in 39 (41 %) and in 35(36.84%) children, respectively. Another three (3.1%) children had received excessive doses and 21 (22%) received therapy for prolonged periods. The common steroid side effects observed were Cushingoid appearance (67.6%), hypertension (26%), gastrointestinal symptoms (7.2%) and growth failure (6%).

None of them had shown haematuria following cyclophosphamide therapy (hemorrhagic cystitis). Of the 107 children, 23 had received adjunctive cyclophosphamide therapy prior to referral. In this group adequate doses were administered in 17 (72%) subjects, where the duration was optimum in only eight (34%) cases. Five (21.73%) children had received therapy for longer duration and three in excessive doses.

The qualified medical practitioners had referred all the children to us. General practitioners accounted for only 32.63% (n=31), while majority of children were treated by pediatrician 36.84% (n=35), and 30% (n=29)% adult physicians, prior to referral. The appropriateness of therapy of the referring physicians in terms of dose and to duration is depicted in Fig.-2. Of the 35 children in whom paediatricians were the primary physicians, treatment was appropriate in 26(74%), while nine (26%) had received inappropriate (inadequate /excessive) therapy. In contrast, appropriate therapy had been administered in only 19% cases by general physicians. Twenty one (72%) of cases treated by adult Physicians was inappropriate.

Children were classified according to their response to steroid therapy and infrequent relapsers constituted 33% of the cases. Frequent relapser comprised 23.75% of children while another 35% were steroid dependent. Initial non-responders and subsequent non-responders accounted for 5.6% and 03% respectively.

Kidney biopsy was done in 42 children. Minimal change disease (MCD) was the commonest histopathological lesion in the patient with idiopathic nephrotic syndrome, accounting for (62%) of the biopsied cases. The other common causes were focal segmental glomerulosceerosis (26%), membrano-proliferative glomerulonephritis (7.14%) and mesangial proliferative glomerulo nephritis (4.76%).

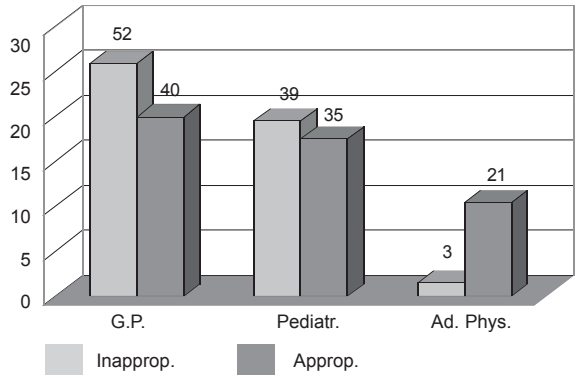

Fig.-1 : *Dose and duration of steroid therapy administered by primary physicians in children with Nephrotic Syndrome.*

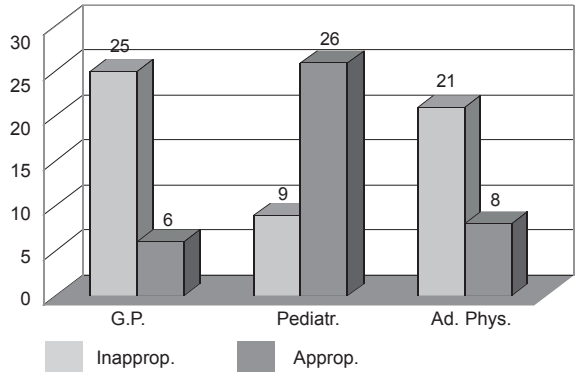

Fig.-2 : *Appropriateness of therapy of the primary physicians.*

Discussion

In children MCD predominates where other histological entities are rare[11]. Cortocosteroid are considered to be the drug of choice in MCD. In the ISKDC study it was found that by the end of eight weeks, there were only about 08% of children who did not respond to steroids[10]. The primary care physicians can easily manage majority of the cases. Steroids and cyclophosphamide are both potentially toxic drugs. Inadequate doses on the other hand may not only be associated with a lower response rate but also adversely effect the course of the illness.

Current evidence suggests that treatment of the initial episode influence the subsequent courses of the illness. The intensity of initial treatment may decrease the rate of subsequent relapse and long lasting subsequent remission[6,9]. Thus, it is imperative for the treating physician to adhere to the standard protocol.

The spectrum of idiopathic nephrotic syndrome in this series is similar to that reported from western countries[12].

Data regarding steroid therapy prior to referral shows only 54.73% of children had received steroid therapy in standard doses and 42% for adequate duration. Physicians had a tendency to use repeated courses of steroids in inadequate doses for shorter periods resulting in greater side effects and lower response rate. This could account for the fact that the majority of the patients behaved as steroid dependent. A large proportion of these referred patients could otherwise have been easily managed at the primary level had they been treated with appropriate regimens. Data regarding previous cyclophosphamide therapy was analyzed and it was found that therapy in recommended doses and duration had been given in 72% cases and 34% cases, respectively.

Three of them had been administered cyclophosphamide in doses exceeding the gonadotoxic dose (>304mg/kg)[13].

Qualified medical practitioners had referred all the children. Majority of them had been referred to us by general practitioners (32.63%) and (36.84%) pediatricians, respectively.

On evaluation of the therapy by different physician prior to the referral it was found that treatment was inappropriate by 81% general practitioners and 72% adult physician.

These finding highlights the lacunae in the current state of knowledge amongst the primary care physicians and underscores the need for greater awareness regarding the therapy of children with nephrotic syndrome. With this awareness one can decrease the frequency of drug related side effects and lower the frequency of relapses.

References:

1. White RHR, Glasgow EF, Mills RJ. Clinico-pathological study of nephrotic syndrome in Children. Lancet 1970; 1 : 1299-1302.
2. Brodehl J. Conventional therapy for idiopathic nephrotic syndrome in children, Clinical Nephrol 1991, 35 : S8 -S15.
3. Arbeitsgemeinschaft Fur Padiatrische Nephrologie. Short versus Standard prednisone therapy for initial

treatment of idiopathic nephrotic syndrome in children Lancet 1988,1 : 380 -383.

4. Hodson E, Knight J F, Wills NS, Crag JC. Corticosteroid therapy in nephrotic syndrome. A meta - analysis of randomized controlled trials. Arch Dis child 2000; 83 : 45-51.
5. Arbeitsgemeinschat Fur Padiatrische Nephrologie. Alternate day versus intermittent prednisone in frequently relapsing nephrotic syndrome. Lancet 1979, 1 : 401 - 403.
6. Tavis LB. The nephrotic syndrome. Rudolph AM, Hoffinan JIE. In Pediatrics, Eighteenth edition Connecticut: Appleton and Lange, 1987.pp 1176-1185.
7. Nash AM, Edelmann Jr CM, Bernstein J, Barnett HC. Minimal change nephrotic syndrome, diffuse mesangial hypercellularity and focal glomerular sclerosis. In: Pediatric Kidney Disease, second edition: Boston: Little Brown and Co, 1992, pp- 1267 - 1290.
8. Glassock RJ, Adler, SG, Ward HJ, Cohen AH. Primary glomerular disease. In: The Kidney, Fourth edition. Edn Philadelphia: WB Saunders Co. 1991. pp 1182 - 1279.
9. Arbeitsgemeinschaft. Fur Padiatrische Nephrologie. Minimal change nephrotic syndrome: long prednisone versus standard prednisone therapy. Pediatr Nephrol 1990; 4(c) : 60.
10. International Study of Kidney Disease in Children, The primary nephrotic syndrome in children: identification of patiens with minimal change nephrotic syndrome from initial response to prednisone. J Pediatr 1981; 98 : 561 - 564.
11. Brodehl J. Nephrotic syndrome in children: Diagnosis and treatment. World Pediatrics Child Care 1986; 1 : 9- 18.
12. Srivastava RN, Mayekar G, Anand R, Choundary VP, Ghai OP, Tandon HD. Nephrotic syndrome in Indian children. Arch Dis Childhood 1975; 50 : 626-630.
13. Brodehl J. Conventional therapy for idiopathic nephrotic syndrome in children. Clinical Nephrol 1991; 35 : S8-S15.