TREATMENT OF NEPHROTIC SYNDROME

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ABSTRACT

There are well defined therapeutic protocols for childhood nephrotic syndrome. Appropriate therapy helps in minimizing side effects besides decreasing referrals to tertiary care centres. We have analysed the appropriateness of therapy of primary care physicians in 111 children with nephrotic syndrome referred to our Institute from January 1989 to December 1991. Prednisone was administered in adequate doses in 51 (52.6%), and for adequate duration in 41 children (42.2%). Adjunctive cyclophosphamide therapy was administered in the recommended doses and duration in 33% of the cases. On evaluation of the therapy it was observed that inappropriate treatment had been administered by 39.4% of the pediatricians, 59% of internists and 80% 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.

Key words: *Nephrotic syndrome, Chemotherapy.*

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Nephrotic syndrome is a common problem in children. Minimal change disease (MCD) is the commonest histopathological variety(l). This has an excellent response to steroids and as a result of several controlled trials, there has been a continued evaluation and improvement of existing protocols(2-8). 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(9). Appropriate therapy helps in minimizing side-effects. Moreover, it has now been demonstrated that the adequacy of initial therapy effects the subsequent course of the illness(4,9). We conducted a study to analyse the appropriateness of therapy given by the primary physicians in children with nephrotic syndrome prior to their referral to our institute.

Material and Method

The study group comprised of all children with nephrotic syndrome referred to our institute from January 1989 to December 1991. During this period 111 children with nephrotic syndrome were seen in our Outpatient Department. Our institute is a tertiary care centre which caters exclusively to the referred cases. The referring physicians comprised general practitioners, internists and pediatricians. At the initial visit besides clinical examination, a detailed evaluation of treatment history was carried out to find out the appropriateness of therapy of the referring physicians in terms of the dose and the duration of prednisone and cyclophosphamide. The currently recommended treatment protocol by the German APN (Arbeitsgemeinschaft Fur Padiatrische Nephrologie) group for the initial episode and relapse was taken as the standard for comparison. The therapy of initial episode comprises of Prednisone in doses of 60 mg/m^2/day x 4 weeks followed by 40 mg/m^2/

alternate day x 4 weeks. A relapse is treated with the same drug in a dosage of 60 mg/m^2/day till remission (documented for 3 days) followed by 40 mg/m^2/alternate day x 4 weeks(3-7). Cyclophosphamide is administered in doses of 2 mg/kg/day for 8 and 12 weeks in frequent relapsers and steroid dependent patients, respectively(8).

The name, address and qualifications of the referring physicians were duly recorded. Urinary examination and blood biochemical investigations were done in all the patients. The diagnosis of nephrotic syndrome was based on the standard ISKDC criteria(2). All patients were treated with oral prednisone therapy as per the standard APN protocol. Kidney biopsies were carried out if: *(i)* age was less than 1 year and more than 8 years; *(ii)* no response to 8 week course of steroid therapy; *(iii)* frequent relapsers and steroid dependent children prior to initiating cytotoxic therapy, and *(iv)* unusual clinical features (sustained hypertension, gross hematuria) or cases showing hypocomplementemia, microscopic hematuria and elevated blood urea and creatinine.

Based on their subsequent response to adequate steroid therapy, these patients were categorized as frequent relapsers (FR), steroid dependent (SD), initial nonresponders (INR) and subsequent non-responders (SNR) Using standard case definitions(5). Children who responded to the steroid regimen, but had a duration of follow up of less than 6 months were categorized as responders (R).

Results

Of 111 children there were 78 boys and 33 girls. The age of onset of disease was 4.4 years (range 1-16 years), and the mean age at referral was 6.8 years (1.5-16 years). The duration of follow up at the Institute ranged from 2 to 30 months (mean of 24 ± 5.5 months).

Of the 111 children, 101 (97%) had received steroids prior to referral while 15 (13.5%) had also been treated with oral cyclophosphamide. Of these, accurate details of previous therapy regarding duration and dosage were available in 97 children. The distribution of these children based on the adequacy of dose and duration of the previous steroid therapy is depicted in *Fig 1*. Only 51 (52.6%) children had received steroids in appropriate doses and 41 (423%) had received therapy for appropriate duration prior to the referral. In contrast inadequate therapy in terms of dose and duration had been given in 41 (42.3%) and in 39 (40.2%) children, respectively. Another 5 (5.1%) children had received excessive doses while 17 (173%) of them had received therapy for prolonged periods. The common steroid side-effects observed were Cushingoid appearance (56.7%), hypertension (28.9%) and GI symptoms (5.1%) None of them had shown hematuria following cyclophosphamidevtherapy (hemorrhagic cystitis). Of the 111 children, 15 had received adjunctive cyclophosphamide therapy prior to referral. In this group adequate doses were administered in 9 (60%) subjects, while duration was optimum in only 5 (33%) children. Inadequate therapy in terms of dose and duration had been given in 5 (33%) and 8 (533%) children, respectively. Two (13.3%) children had received therapy for longer duratien and one child in excessive doses.

All the children had been referred to us by the qualified medical practitioners. General practitioners accounted for only 25.8% (n=25), while majority of children were treated by internists (40.2%) and pediatricians (34%) prior to referral. The appropriateness of therapy of the referring

physicians in terms of dose and duration is depicted in *Fig. 2.* Of the 33 children in whom pediatricians were the primary physicians, treatment was appropriate in 20 (60.6%).while 13 (39.4%) had received inappropriate (inadequate/excessive) therapy. In contrast appropriate therapy had been administered in 41% (n=16) and 20% (n=5)

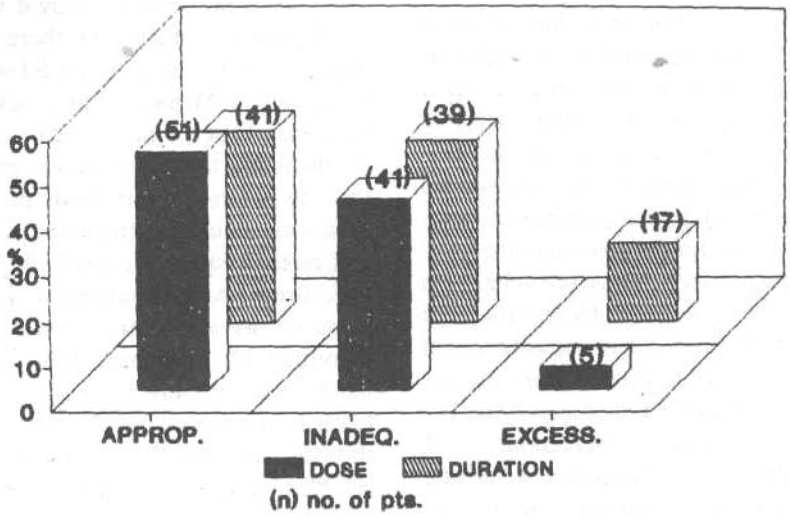

Fig. 1. Dose and duration of steroid therapy administered by primary physicians in children with nephrotic syndrome.

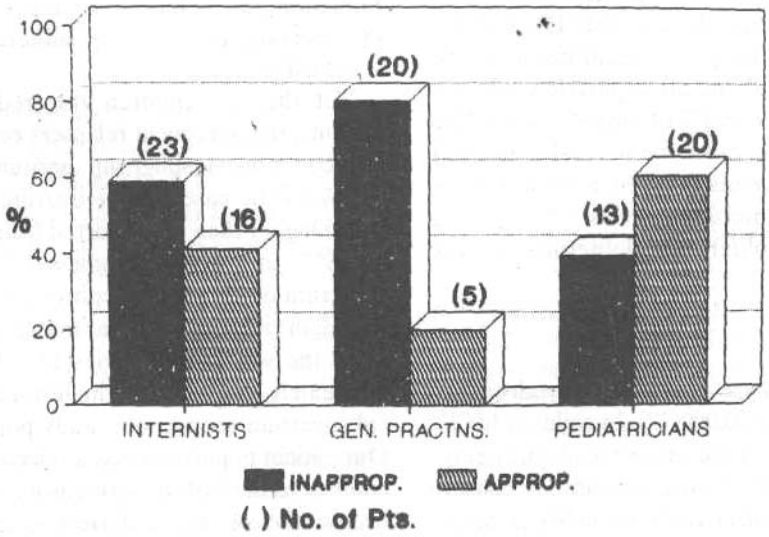

Fig. 2. Appropriateness of therapy of the primary physicians.

of the children treated by internists and the general practitioners, respectively. Fifty nine per cent of cases treated by internists and 80% of these treated by general practitioners had received inappropriate therapy *(Fig. 2)*.

When the distribution of these children according to their response to steroid therapy was analysed it was observed that infrequent relapsers constituted 34.5% of the cases. Frequent relapsers comprised 25% of children while another 28% were steroid dependent. Initial non-responders and subsequent non-responders accounted for 8.5% and 4.0% respectively. Thus, the subgroups which pose therapeutic problems (frequent relapsers, steroid dependent and subsequent non responders) accounted for smaller proportion of the referred cases. Of the 111 children kidney biopsies were done in 51 children. Primary or idiopathic nephrotic syndrome was the commonest, accounting for 104 of the 111 children (93.8%) while secondary causes were seen in 7 children: congenital nephrotic syndrome in 4 and HSP, SLE and amyloidosis in one case each. Minimal change disease (MCD) was the commonest histopathological lesion in the patients with idiopathic nephrotic syndrome accounting for 58.9% of the total cases. The other common causes were focal segmental glomerulosclerosis (23.5%), membranoproliferative glomerulonephritis (7.8%), and mesangial proliferative glomerulonephritis (5.9%).

Discussion

The incidence of nephrotic syndrome is reported to 2/100,000(12). In children MCD predominates while other histological entities are rare(10). Corticosteroids are considered to be the drug of choice in MCD. Since 1960 there have been several controlled trials by the ISKDC and German APN groups(2,3,8). Besides defining clearly the nature, course and prognosis, they have helped in establishing well defined therapeutic guidelines(4). Consequently, the mortality has decreased from 16% to between 3% and 7%(12). In the ISKDC study it was found that by the end of 8 weeks, there were only about 8% of the children who did not respond to steroids(2). Majority of the cases can easily be managed by the primary care physicians. At the same time they should ensure that they do not create iatrogenic problems, in what is essentially a benign disease. Steroids and cyclophosphamide are both potentially toxic drugs. A wide variety of side effects, some of them life threatening have been reported(6,12). Inadequate doses on the other hand may not only be associated with a lower response rate but also adversely affect the course of the illness. It has now been established that the intensity of initial treatment has a decisive influence on the subsequent rate of relapse—the more aggressive the initial therapy, the lower the relapse rate thereafter and long lasting the subsequent remission(5,8). Thus, it is imperative for the treating physician to adhere to the standard protocol.

Of" the 111 children referred to our institute, the infrequent relapsers constituted the commonest subgroup accounting for 34.6% of the cases. Their distribution was much higher than the reported frequency of 15-18% in various studies(10,13). The spectrum of idiopathic nephrotic syndrome in Indian children is similar to that reported from the western countries(14). This was adequately confirmed by the histopathological spectrum seen in our study population. Our patient population was a selected one in contrast to the ISKDC series as it comprised exclusively of the referred cases only. Moreover, there are reports that frequent relapsers may be more common in India(11).

When the data regarding steroid therapy prior to referral was analysed, we found that only 52.6% of children had received steroid therapy in standard doses and 42.2% for adequate duration as per the APN protocol. Physicians had a tendency to use repeated courses of steroids in inadequate doses and for shorter periods resulting in greater side effects and lower response rate. This could account for the fact that the majority of our patients behaved as infrequent relapsers on follow up. A large proportion of these referred patients could otherwise have been easily % managed at the primary level had they been treated with appropriate regimens. .

When the data regarding previous cyclophosphamide therapy was analysed it was found that therapy in recommended doses and duration had been given in 60% and 33% of the referred children, respectively. Two of the 15 children had been administered cyclophosphamide in doses exceeding the gonadotoxic dose (>300 mg/kg)(9).

All the children had been referred to us by qualified medical practitioners. Majority of them had been referred to us by internists (40.2%) and pediatricians (34%). None of our patients had been referred by a nephrologist. On evaluation of the therapy by different physicians prior to the referral it was found that treatment was inappropriate by 39.4% of the pediatricians, 59% of the internists and 80% of the general practitioners. Thus, there was a high incidence of inappropriate therapy even amongst pediatricians.

These findings highlight 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. (The onus for this is on the tertiary care institutes, medical colleges and scientific academies like the Indian Society of Nephrology and Indian Academy of Pediatrics. This would improve the quality of life of these patients by decreasing the frequency of iatrogenic drug related side-effects and lower frequency of relapses.

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