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Brief report

Nephrotic syndrome in Saudi children clinicopathological study of 150 cases

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Abstract. The study includes 150 children with primary nephrotic syndrome (NS), aged 16 months to 13 years with a median age of 5 years. The male to female ratio was 2:1 and the familial occurrence was 6%. Amongst 48 biopsied patients, 19 (39%) had focal segmental glomerulosclerosis, 17 (35%) had diffuse mesangial proliferative glomerulonephritis (MesPGN) and 10 (21%) had minimal change nephropathy. About 90% of patients responded to the initial prednisolone therapy. Subsequently 45% of steroid-sensitive patients had frequent relapses, 23% had no relapses, 21% had infrequent relapses and 5% became steroid resistant. Saudi children with primary NS showed no differences as regards age at onset, male predominance and response to initial prednisolone therapy when compared with published data from other countries. However, the higher incidence of familial occurrence, the relatively high frequency of MesPGN, the rarity of infection-related NS and a decreasing incidence of serious infections with improving socio-economic status were all noteworthy.

Key words: Nephrotic syndrome – Minimal change nephrotic syndrome – Focal segmental glomerulosclerosis – Mesangial proliferative glomerulonephritis – Steroid therapy

Introduction

Primary nephrotic syndrome (NS) is one of the commonest renal problems in childhood. Renal biopsies of affected patients show minimal change nephropathy (MCN) in 65–85% of cases with focal segmental glomerulosclerosis (FSGS) as the second most common finding in 7–11% of cases [1]. The remaining patients have rarer types of glomerular lesions such as diffuse mesangial proliferative glomerulonephritis (MesPGN), membranous glomerulonephritis (MGN) and membranoproliferative glomerulonephritis (MPGN). These histopathological variations determine to a greater extent the patient's response to steroids and the long-term prognosis. Patients with a minimal change show better response to steroids and carry an excellent long-term prognosis compared with patients with FSGS, who are unlikely to respond to steroids and have a guarded prognosis [2].

In Saudi Arabia, very little is known about the clinicopathological features of childhood NS. The creation of our renal unit about 4 years ago in the busiest children's hospital in the kingdom gave us an opportunity to study the clinical profile, histopathological presentation and response to prednisolone therapy in affected children.

Patients and methods

One hundred and fifty children with primary NS were referred to us over a period of 3 years between January 1986 and 1989. Children with congenital or infantile NS, or those with crescentic glomerulonephritis were excluded from the study. All patients received standard initial prednisolone therapy, either in the referral hospital or in our unit. In our unit treatment, including that of relapses, was in accordance with the therapeutic regimen adopted by the International Study of Kidney Diseases in Children, ISKDC [2].

Definitions. The definitions used in the study were modified from the ISKDC [3], and are described below.

NS: the presence of heavy proteinuria ($\geq$40 mg/h per m^2, hypoalbumineamia ($\leq$25 g/l and oedema.

Response: urine remaining free of proteins on semi-quantitative testing (Medi-test Combi 6, Macherey-Nagel, D-5160, Düren, FRG) for at least 3 consecutive days.

Relapse: 3 consecutive days of heavy proteinuria (3+) as demonstrated by semi-quantitative testing (Medi-test Combi 6). Episodes of proteinuria occurring with infections and disappearing without any additional treatment were not included.

Frequent relapses: two or more relapses in the 6 months following initial prednisolone therapy or four or more relapses in any 12-month period.

Early steroid resistance: failure to respond to an 8-week course of prednisolone therapy.

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Table 1. Indications for kidney biopsy and histopathological diagnosis

Indication for biopsy	Histopathological diagnosis					Total
	FSGS	MesPGN	MCN	FGS	MGN	
Steroid resistance						
Early	8	3	1	–	1[a]	13
Late	4	2	1	–	–	7
Frequent relapses on maintenance steroids	7	12	8	1	–	28
Total	19 (39%)	17 (35%)	10 (21%)	1 (2%)	1 (2%)	48 (100%)

FSGS, Focal segmental glomerular sclerosis; MesPGN, diffuse mesangial proliferative glomerulonephritis; MCN, minimal change nephropathy; FGS, focal global sclerosis, MGN, membranous glomerulonephritis

[a] Hepatitis B surface antigen positive

Late steroid resistance: resistance to prednisolone therapy after an initial response.

Kidney biopsy. Kidney biopsy was performed in patients with early or late steroid resistance and in those with frequent relapses despite maintenance prednisolone therapy of 0.5 mg/kg on alternate days. Percutaneous renal biopsies were performed with "Tru-cut" disposable needles using intravenous urography or ultrasonography for renal localization. Open biopsies were performed in 4 patients, 3 with solitary kidneys and 1 with a dysplastic kidney. The tissue obtained was processed for light microscopy, immuno-fluorescence, and in selected cases electron microsopy.

Results

The 150 children with primary NS included 103 males and 47 females. Their ages at the onset of illness ranged from 16 months to 13 years with a median age of 5 years. Nine patients had a family history of NS in another sibling.

Infections

Four patients were positive for hepatitis B surface antigen. Two had pneumococcal peritonitis and 1 had septic arthritis. None of the patients had schistosomiasis or malaria.

Renal histopathology

Forty-eight kidney biopsies were performed in an equal number of patients. Indications for renal biopsy and the histopathological diagnoses are shown in Table 1.

Response to prednisolone therapy

All patients received prednisolone therapy and 137 went into remission but 13 proved steroid resistant. The latter included 8 patients with FSGS, 3 with MesPGN and 1 each with MCN and MGN. During the follow-up period of 13 months to 3 years, 61 steroid-sensitive patients had frequent relapses, 31 had no relapses, 28 had infrequent relapses and 7 became steroid resistant. Ten patients were lost in the follow-up period.

Discussion

NS in Saudi children, as anywhere else in the world, is one of the commonest renal problems. A majority of our patients were referred from different parts of the country. This therefore constitutes a selected group from which the overall incidence throughout the kingdom cannot be extrapolated. The male predominance and the age distribution of the illness is similar to children in other countries [1].

Six percent of our patients had a family history of the disease in another sibling; a high incidence when compared with a reported incidence of about 2% [4]. We believe that it may be even higher as we did not include families where the siblings or one of the parents probably had or even died from NS many years previously, and no documentation was available to confirm the diagnosis. A high incidence of familial cases in the local population is most probably due to a very high rate of consanguineous marriages.

Some of our referred cases suffered more from the toxic effects of steroid therapy than the NS itself. Of the 73 patients who received steroids prior to referral 40 (60%) had a severe cushingoid appearance. This was associated with mild to moderate hypertension in 10 cases, glycosuria in 3 cases, and stunted growth in 17 cases, diagnosed on the basis of "catch-up" growth after decreasing or withdrawing steroids. These toxic effects were a result of high-dose steroids used in order to keep frequently relapsing patients in remission, or prolonged steroid therapy in resistant cases. All patients recovered after the steroids were withdrawn or reduced with or without the help of cyclophosphamide therapy.

All our patients were investigated for infection-related NS which is common in neighbouring East African countries [5]. None of the patients suffered from malaria or schistosomiasis which exist in certain areas of the kingdom. Four cases of hepatitis B infection were detected which is compatible with its local incidence [6]. A significant decrease was seen in the incidence of life-threatening "secondary" infections compared with the high incidence reported in 1982 [7]. This is most probably due to a dramatic improvement in the socio-economic conditions and health care facilities. Induction of longer remissions with cyclophosphamide therapy may also have played a role.

About 35% of our biopsied patients had MesPGN, characterized by diffuse mesangial cell proliferation, increase in mesangial matrix, normal glomerular capillary walls, no extracapillary or endocapillary proliferation, and mesangial IgM deposition [1, 8, 9]. The clinical presentation of this group was no different from those with FSGS or MCN and it is not the purpose of this paper to discuss its significance or prognostic implications. The relatively higher incidence of MesPGN seen in our patients is consistent with the incidence previously reported in Saudi children with steroid-resistant NS [10]. Similar findings have also been reported from other developing countries [5, 11]

and this raises the possibility that it may be related to a higher incidence of non-specific infections in these countries. Racial factors, however, are difficult to exclude.

Lastly, response to initial prednisolone therapy and the subsequent course of our patients was similar to published reports from other countries [3, 12]. About 90% of the patients proved steroid sensitive, of whom about 23% had a permanent remission, 45% had a frequent relapsing course, 21% had infrequent relapses and 5% became steroid resistant.

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Ask the expert*

Is it correct to supplement patients with nephrotic syndrome with vitamin D and calcium?

Key words: Nephrosis – Vitamin D

In 1974, Schmidt-Gayk et al. [1] reported for the first time that the serum concentration of 25-hydroxy-vitamin D [25(OH)$_2$D] is lowered in patients with nephrotic syndrome (NS). The reason for this is a loss of 25(OH)D bound to its carrier protein in the urine. Alterations in the level of circulating 1,25(OH)$_2$D, which shares the same carrier protein, have also been reported [2], but have not been uniformly confirmed [3]. Available assays for estimation of vitamin D concentration measure total vitamin D, whereas only the free (unbound) 1,25(OH)$_2$D will bind to its receptor. Auwerx et al. [4] have measured the concentration of both vitamin D and vitamin D binding protein and calculated a low concentration of free 1,25(OH)$_2$D in adults with NS. On the other hand, patients with NS and a normal glomerular filtration rate do not show biochemical signs of metabolic bone disease. Serum calcium (Ca) is low due to a reduced concentration of serum albumin, but elevation of serum alkaline phosphatase and parathyroid hormone is usually not noted. There are very preliminary reports of the bone morphology of patients with NS [5, 6]. Malluche et al. [5] found evidence of slightly defective mineralisation and parathyroid overactivity in two of three adult patients, while others observed normal bone histology [6]. Intestinal Ca absorption was noted to be low in metabolic balance studies [7], but it was generally normal when measured with radioactive Ca [2, 8] or stable Ca isotopes [8].

All findings taken together argue strongly against the necessity of routine treatment of children with long-standing steroid-sensitive or steroid-resistant NS with vitamin D and/or Ca. In the study of Mehls et al. [8] vitamin-D-dependent intestinal Ca absorption was investigated in children with a median age of 10 years (range 6–15 years). The steroid-resistant NS lasted up to 3.5 years (proteinuria ranging from 1.4 to 4.2 g/day). It has to be proven whether vitamin D treatment is necessary after a longer duration of steroid-resistant NS or in patients with a persistently very high level of proteinuria (e. g. above 10 g/day). Vitamin D treatment is definitely necessary as soon as one of these patients shows signs of chronic renal failure. In these patients, we have measured a decreased cumulative intestinal Ca absorption (O. Mehls, unpublished work).

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* The editors invite questions for this section