Original Article

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An Estimation of Steroid Responsiveness of Idiopathic Nephrotic Syndrome in Iranian Children

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Abstract

Objective: Idiopathic Nephrotic syndrome (INS) is the most common form of nephrotic syndrome (NS) in children with the potential of progression to end stage renal disease (ESRD). INS is steroid-responsive in most children, but not all patients respond to it. The aim of this study was to determine the rate of steroid responsiveness in children with INS that referred to Children's Medical Center since 1995 to 2007.

Methods: In as a cross sectional study, the medical records of all children with INS aged 1 to 15 years who were referred to our referral hospital was reviewed. All patients with onset of disease less than 1 year of age, spontaneous remission, secondary forms of NS associated with systemic diseases, and follow up duration of less than 12 months were excluded from the study. Patients were categorized into 6 groups: Group 1 needed biopsy prior to any treatment, group 2 non-relapsing NS, group 3 infrequently relapsing NS, Group 4 frequently relapsing NS, group 5 steroid dependent NS and group 6 steroid resistant NS.

Findings: A total of 238 patients were enrolled in the study. Kidney biopsy was performed in 79 cases. Minimal change lesion (MCL) was the most common (36.7%) pathological diagnosis. Steroid responsiveness was found in 81.5% of all cases including: 96% of MCL (consisting of biopsy proven cases and presumed ones), 32% of focal and segmental glomerulosclerosis, 73% of diffuse mesangial proliferation and 58% of membranoproliferative glomerulonephritis patients. During minimal follow up period of 12 months, there were 194 patients in remission, 32 patients with active NS, and 12 patients in ESRD.

Conclusion: Our study results showed that 81.5% of all patients, 96.2% of MCL and 32% of FSGS patients initially responded to steroid therapy.

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Key Words: Idiopathic Nephrotic Sndrome; Steroid Responsiveness; Glomerulonephritis ; FSGS

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Introduction

Idiopathic nephrotic syndrome (INS) is the most common form of NS in children with the potential of progression to end stage renal disease (ESRD)[1]. It is more common in boys than in girls with a ratio of 1.6:1 and occurs in children at a median age of 4 years[2]. The mortality rate of nephrotic syndrome (NS) was 40% before 1940, primarily due to infection; but this has been significantly reduced with the introduction of steroid treatment and antibiotics. Steroids have long been used as the first line of treatment in NS, however, other immune-suppressives may be indicated when prednisolone fails to induce or sustains remission[3].

The overall incidence of childhood INS has been generally stable over the past three decades (two to seven cases per 100,000 children)[3]. However, the histological pattern of childhood INS is changing, and the incidence of FSGS seems to be increasing[4,5]. Histopatho-logical findings in NS may reflect in patterns of responsiveness[1]. The most common form of NS in children is minimal change lesion (MCL)[6,7]. The vast majority of patients with MCL (>90%) respond to steroid therapy. Other types of INS like focal and segmental glomerulosclerosis (FSGS), diffuse mesangial proliferation (DMP), membranoproliferative glomerulonephritis (MPGN) and membranous glomerulonephritis (MGN) are less steroid-responsive. More than 90 percent of patients who respond to steroid therapy have MCL[6]. MCL can accurately be diagnosed based on presenting clinical findings in children younger than 6 years of age, absence of hypertension, absence of hematuria, normal complement levels, and normal renal function[1].

Corticosteroids play a key role in the treatment of INS. Although a high proportion of patients experience relapses, many of them continue their steroid responsiveness. The International Study for Kidney Diseases in Children (ISKDC) first introduced an empirical treatment protocol for INS which later faced some minor changes. The ISKDC recommends that the initial episode be treated with prednisolone at a daily dosage of 60 mg/m^2 for 4 wk, followed by 40 mg/m^2 for 3 days out of a week (intermittent therapy) for another 4 wk[8,9]. Roughly 95% of patients with MCL and 20% with FSGS achieved remission with this protocol [2,3]. Approximately 90% of patients who will respond to steroids (urine trace or negative for protein for 3 consecutive days) do so within four weeks after starting steroids[10].

Majority of children with INS experience relapses (proteinuria >40mg/m^2/hr or urine protein test tape 3+ or more for 3 consecutive days after achieving remission) which could be categorized as infrequent relapsing NS (IFRNS): less than 3 relapses during 1 year after achieving remission, Frequent Relapsing NS (FRNS): 3 or more relapses during 1 year after achieving remission, and steroid dependent NS (SDNS): 2 consecutive relapses during steroid therapy or within 2 weeks after discontinuation of therapy.

On the basis of response to empiric glucocorticoid therapy, patients with INS can be classified into Glucocorticoid-Responsive and Glucocorticoid-Resistant. Resistance to steroid therapy represents 10% of INS[11]. Gulati et al by reviewing histopathology of 136 steroid resistant NS (SRNS) children found that FSGS was the most common cause of SRNS in children with onset of NS at all age groups[12], also Kari in Saudi Arabia[13] reported the same results. Del Rio et al by reviewing the previously published data on SRNS in literature showed a rise in the incidence of FSGS[4]. A literature review of steroid-sensitive NS (SSNS) by Hodson et al indicated that the mechanism of steroid sensitivity is due to lymphocyte-derived circulating factors leading to podocyte injury with subsequent proteinuria[14].

The current study aimed to define the true steroid responsiveness pattern of Iranian children with INS, since there is not much statistical information regarding this issue in Iranian children.

Subjects and Methods

The study was conducted as a cross sectional retrospective descriptive study. The medical records of all children with INS aged 1 to 15

years who were referred to the hospital since 1995 to 2007 were reviewed. Cases were selected in a non random simple fashion. Medical records of patients with INS who fulfilled the study criteria were the source of information.

Exclusion criteria were age of onset of disease less than 1 year, secondary forms of NS, less than 12 months follow-up, and initial spontaneous remission. In each patient clincopathological findings, responsiveness to employed treatments, and outcome or status at the follow up period of at least 12 months was determined.

Renal biopsy was performed prior to treatment in those with the onset of the disease occurred at >7 years of age, hypertension, renal failure, macroscopic or high grade microscopic hematuria, low C_3 level, family history of Alport syndrome, and in steroid unresponsive patients at any time during the course of treatment.

Prednisolone was administered at a dosage of 60 mg/m^2/day (maximum 80mg/day) three times a day for 4 weeks; in the case of remission, it continued at the dosage of 40mg/m^2/day every other day for another 4 weeks and then tapered 10mg/m^2 each 2 weeks in all patients except MPGN cases. Patients with MPGN were treated with prednisolone at the dosage of 20-30 mg/m^2/day plus dipyridamole 2-3 mg/kg/day for 2 years.

On the basis of the steroid responsiveness pattern and the necessity of kidney biopsy prior to initial treatment, patients were categorized into 6 groups: Group 1: those needed renal biopsy prior to initial treatment, Group 2: non relapsing NS patients (NRNS) (no relapse in at least 12 months after discontinuation of initial therapy), Group 3: IFRNS (less than two relapses within 6 months or three relapses during 1 year after achieving remission), Group 4: FRNS (two or more relapses within 6 months or three or more during 1 year after achieving remission), Group 5: SDNS (two consecutive relapses during tapering of steroid therapy or within 2 weeks after discontinuation of therapy), and Group 6: SRNS.

Data were analyzed using the Statistical Package of SPSS (version 17). Descriptive statistics were used, such as mean±standard deviation (SD) for continuous variables and percentage (%) to describe the proportion of categorical variables such as sex and the frequency of different histopathological diagnosis.

Findings

A total of 282 patients initially entered the study; 44 cases were excluded due to inadequate follow up (34 cases), secondary forms of NS (8 cases) and spontaneous remission (2 cases). Finally 238 patients remained in the study.

The age range of patients was 1-15 years with an average onset of 4.52 years. There were 152 (63.8%) males and 86 (36.2%) females. The male/female ratio was 1.76 in this study. Sex distribution of our six study groups is summarized in Table 1. Range of follow up period was 12-144 months with a mean of 51 months.

Prior to the initial treatment, kidney biopsy was performed in 35 patients on the basis of one or two indications (family history of Alport syndrome in 1 case, high grade microscopic hematuria in 23 cases, onset of the disease occurred at >7 years of age in 22 cases, hypertension in 9 cases, decreased complement level in 7 cases, and renal failure in 5 cases; 17 cases had more than one indication for renal biopsy).

Prednisolone was administered in the remainder 203 patients without initial renal biopsy, but later in the course of treatment 44 of these patients underwent renal biopsy (Group 4: 13 cases, Group 5: 13 cases, and Group 6: 18 cases). Renal biopsy is performed in totally 79 patients. Histopathological diagnoses were MCL in 29 patients (36.7%), FSGS in 22 patients (27.8%), DMP in 11 patients (13.9%), MPGN in 12 patients (15.1%), and others (MGN: membranous glomerulonephritis, Alport syndrome, FPGN: focal proliferative glomerulonephritis) in 5 patients.

Histopathological diagnoses were MCL in 29 patients (36.7%), FSGS in 22 patients (27.8%), DMP in 11 patients (13.9%), MPGN in 12 patients (15.1%), and others membranous glomerulonephritis (MGN), Alport syndrome,

Table 1: Characteristics of groups of patients with nephritic syndrome on the basis of the steroid responsiveness

Group	No (%)	Male	Female	Histopathological diagnosis on renal biopsy	Status after the follow up period
1*	35 (14.7)	21	14	MCL: 13; FSGS: 5; DMP: 5; MPGN: 11; Alport: 1	Remission:19; active disease: 12; ESRD: 4
2 (NRNS)	45 (18.9)	32	13	-	Remission: 45
3 (IFRNS)	44 (18.4)	30	14	-	Remission:44
4 (FRNS)	39 (16.3)	25	14	MCL: 7; FSGS: 3; DMP: 2; FPGN±: 1	Remission: 37; Active disease: 2; ESRD: 0
5 (SDNS)	47 (19.7)	31	16	MCL: 8; FSGS: 3; DMP: 1; FPGN: 1	Remission:44; Active disease: 3; ESRD: 0
6 (SRNS)¶	28 (11.7)	15	13	MCL: 1; FSGS: 11; DMP: 3; FPGN:1; MGN:1; MPGN:1	Remission: 5; Active disease: 15; ESRD: 8

*Group 1: all patients underwent biopsy before treatment; **NRNS:** non relapsing nephrotic syndrome; **IFRNS:** infrequent relapsing nephrotic syndrome; **FRNS:** frequent relapsing nephrotic syndrome; **SDNS**: steroid dependent nephrotic syndrome; **SRNS:** steroid resistant nephrotic syndrome; **MCL:** minimal change lesion; FSGS: focal and segmental glomerulosclerosis; **DMP:** diffuse mesangial proliferation; **MPGN:** membranoproliferative glomerulonephritis; **MGN:** membranous glomerulonephritis; **FPGN:** focal proliferative glomerulonephritis, **ESRD:** end stage renal disease
¶10 patients were not biopsied, of whom 3 patients experienced ESRD and others were in active disease.

focal proliferative glomerulo-nephritis (FPGN) in 5 patients.

Steroid responsiveness was totally found in 194 patients (81.5%) of whom 175 cases (73.5% of all) were in Groups 2-5, and 19 (7.9% of all) cases in Group 1 (out of 23 patients in Group 1 who received steroids). Group 6 patients (11.7% of total) were not responsive to steroids (Table 1). The steroid responsiveness of the 79 patients with histopathological diagnosis on the basis of renal biopsy is summarized in Table 2.

The most prevalent relapsing patterns of "presumed MCL patients" were 4-10 relapses with a mean follow up period of 60 months in 37 (24.8%) patients, 2 relapses with mean follow up period of 51 months in 26(17.4 %) patients, one relapse with mean follow up period of 35 months in 21 (14%) patients, and 3 relapses with mean follow up period of 54 months in 17 (11.4%) patients.

If we consider total number of MCL cases as 178 cases including biopsy proven ones (29 cases) and "presumed" ones (149 cases) (all patients of Group 2 and Group 3 plus non biopsied cases of Group 4 and Group 5), steroid responsiveness of MCL was 96.2% in this study (171 cases were responsive to steroids and only 7 cases did not respond).

Discussion

The aim of our study was to identify the steroid responsiveness pattern in Iranian children with INS during 12 years. Our study findings showed that majority of children with NS (81.5%) respond to steroid therapy. This finding is similar to other studies in other countries in

Table 2: Steroid responsiveness characteristics of biopsied patients

Histopathological diagnosis	No	Initial steroid responsiveness	Status after the follow up period
MCL	29	22	Remission: 22; active disease: 6; ESRD: 1
FSGS	22	7	Remission: 6; active disease: 12; ESRD: 4
DMP	11	8	Remission: 8; active disease: 1; ESRD: 2
MPGN	12	7	Remission: 7; active disease: 4; ESRD: 1
Others (MGN, Alport syndrome, FPGN)	5	0 (steroid in 3 patients with FPGN)	Remission: 0; active disease: 4; ESRD: 1

Middle East and around Iran, but is less (94%) than that in ISKDC report[11].

Table 3 shows comparison of our findings withthose of other studies. However, there are few studies that reported a smaller rate of steroid responsiveness in INS (66% by Safaei et al[15] and 22.5% by Eke[16]).

Jung Sue Kim et al in 2005 found that the frequency of SRNS in children is higher than reported earlier. During the initial steroid therapy, 71% were steroid-sensitive, 15% steroid-resistant and 14% achieved partial response. The follow up study showed that at least 45% of the children with new-onset NS did not show the typical steroid responsive pattern.

Two factors were associated with developing steroid resistance after initial response: shorter interval to the first relapse (2.2 vs 5.4 months) and the first relapse occurring during the initial steroid treatment[17].

In El Sheikh et al study, 94.5% of the patients underwent kidney biopsy amongst which MCL was the commonest (28.84%) histopathological diagnosis[18]. In a study on the role of histopathology on steroid resistance, Gulati et al found that SRNS children constituted 15.1% of the children referred to their institute[12]. In our study, Kidney biopsy was performed in 33.2% of the cases. MCL was the most common (36.7%) pathological diagnosis. FSGS was found in 27.8%, MPGN in 15.1%, DMP in 13.9%, and other lesions in 6.3% of the patients. MCL was found in 22.2% FSGS in 44.4%, MPGN in 14.8% and other pathologies in 1.5% of steroid resistant cases. By histopathological classification of renal biopsies in patients non-responsive to steroids Zaki et al found MPGN in 55.5%, and FSGS in 33.3% of their cases[18]. In Bircan et al study, DMP and MPGN were frequent histopathological findings[19] and Ahmadzadeh (another study from southern Iran) reported that FSGS was the most common (44%) histopathological finding in non-responding patients [20].

The rate of steroid responsiveness in children with MCL in our study is close to responsiveness rate reported by Srivastava[18]. In Srivastava et al study, 76.5% of the cases were diagnosed as MCL, and nearly all of them (98%) responded to steroids[17]. MCL was the most common proven histopathological diagnosis of studies conducted by Soad El Sheikh in Saudi Arabia[18], Davutoglu in Turkey[21], and Srivastava in India[17], but the predominant histopathological diagnosis in African countries was MGN due to high hepatitis B prevalence[22].

Sharples et al compared the natural history and steroid responsiveness of NS in Asians, Europeans, and Afro-Caribbeans by conducting a retrospective study on 42 patients. The incidence of NS was six fold higher in Asian children. They estimated annual incidence of SRNS 16.9 per 100000 in Asians, 2.6 per 100000 in Europeans, and 3.4 per 100000 in Afro-Caribbeans[23]. This rate in Zaki study from Kuwait has been reported 6 per 100,000 children below 12 years of age[24]. In Bhimma et al investigation steroid sensitiveness was 62%[25]. The usually expected SSNS pattern was uncommon in blacks, and MGN accounted for 40% of cases of which 86.2% were associated

Table 3: Comparison of our study with other studies in Middle East

Study	Country	No of patients	Response to steroid therapy	Infrequent relapsers	Frequent relapsers	Steroid dependents
Zaki et al[24]	Kuwait	55	84	--	16.6	15.2
Bircan et al[19]	Turkey	114	86.9	21.9	16.7	21.9
Davutoglu et al[21]	Turkey	62	79.8	57.1	--	22.6
Ahmadzadeh et al[20]	Iran	231	87	26.4	34.8	--
Safaei et al[15]	Iran	44	66	26.4	38.8	13.5
Gulati et al[26]	India	127	82.7	37.9	21.6	18.1
El Sheikh[18]	Saudi Arabia	55	89.3	21	45	--
Our study	Iran	238	81.5%	25.1	22.2	27

uncommon in blacks, and MGN accounted for 40% of cases of which 86.2% were associated with chronic hepatitis B virus antigenemia. Only 14.4% of blacks had either biopsy-proven steroid-sensitive MCL or SSNS[22].

The rate of responsiveness to steroid therapy in our study is more than African studies[22,25].

There are some major differences when compared with African countries which could be explained by NS histopathological pattern varieties. In our study 25% patients had no relapse, that was fewer than in other studies especially other reports from Iran. This rate in Safaei, Ahmadzadeh and El Sheikh studies was 23%, 37% and 38.8%, respectively[15,18,20].

Conclusion

Our study showed that the rate of responsiveness to steroid therapy is 81.5% which is close to those of several other studies. In addition, 96.2% of MCL and 32% of FSGS patients initially responded to steroid therapy. The rate of non-relapsers in this study was 25%, this is smaller than that reported in other investigations in Iran.

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Conflict of Interest: None

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