Trends in Steroid Response Among Children With Idiopathic Nephrotic Syndrome

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Introduction. Idiopathic nephrotic syndrome (INS) is a common chronic illness in childhood and is initially treated with corticosteroids. Recent reports indicate that the incidence of steroid resistance and focal segmental glomerulosclerosis is on the rise. However, these reports involved different ethnic populations. The purpose of this study was to compare the characteristics of INS in Iranian children in different periods.

Materials and Methods. A retrospective chart review of children admitted with the diagnosis of new-onset INS was performed. Patients were divided into two groups based on date of presentation periods of 1991 to 2002 and 2005 to 2012. Steroid resistance was defined as persistent proteinuria (2+ and more) within 8 weeks of oral corticosteroid treatment.

Results. A total of 238 children included in this study (119 in each group). There was an insignificant decrease in the frequency of steroid resistance, along with an insignificant change in histopathology towards focal segmental glomerulosclerosis.

Conclusions. These findings indicate that in contrast to other reports of INS from various ethnic compositions, a tendency to steroid resistance is still arguable in the population of Iranian children.

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INTRODUCTION

Idiopathic nephrotic syndrome (INS) is the most common chronic kidney disorder in children,[1] and corticosteroids remain the first-line treatment for this syndrome.[2] It is believed that steroid response pattern has a more prognostic value than histopathology in INS.[3] According to the first reports of the International Study of Kidney Disease in Children (ISKDC) in 1978, more than 78% of children with INS are steroid responsive.[4] Minimal change disease (MCD) has been the most common histopathology of INS in children, with an incidence of 77.6% to 88% in various studies.[3] However, some recent reports suggest changing trends in the histopathology of INS towards increasing incidence of focal segmental glomerulosclerosis (FSGS) in both adults and children,[5] but a parallel change in steroid sensitivity is still unknown.[6]

The objective of this study was to search for changes over time in response to steroid treatment and histopathological pattern of INS in a population of Iranian children. To our knowledge, this is the first study comparing the histopathology and response to treatment in Iranian children in two separate time periods.

MATERIALS AND METHODS

A retrospective review of medical records of 238 children with INS admitted to Ali-Asghar Children's Hospital in Tehran was performed. In order to compare the changes in responsiveness to steroid therapy as well as other clinical and

laboratory findings over time, we selected the sample from two separate time periods, and divided the study population into two groups of children treated between1991 and 2002 (group A) and children treated in the second period between 2005 and 2012 (group B). Patients with new-onset primary INS (MCD, diffuse mesangial hypercellularity [DMH], and FSGS) or in the early phase of steroid treatment with at least 2 months of follow-up were included. All patients fulfilled the diagnostic criteria of nephrotic syndrome including generalized edema, massive proteinuria (protein excretion > 50 mg/kg/d or urine protein-creatinine ratio > 2.0), hypoalbuminemia (serum albumin < 2.5 g/dL), and hyperlipidemia. A major limitation of this study was the exclusion a lot of patients for their previous admissions in other medical centers. Exclusion criteria consisted of patients with congenital nephrotic syndrome, low serum complement C3 level, spontaneous remission, and nephrotic syndrome secondary to infections, drugs, systemic diseases, and vascular and metabolic disorders.

Kidney biopsy was performed in children with steroid resistance, gross hematuria, persistent hypertension, low C3 complement level, and low or high diagnostic age, before initiation of cyclosporine treatment and in patients with persistent kidney failure. Microscopic hematuria was defined as 5 or more erythrocytes per high-power field in fresh urine sediment. Hypertension was defined as blood pressure exceeding the 95th percentile, according to relevant age, sex, and height percentile. Kidney failure was defined as 25% decline in kidney function. A serum cholesterol level greater than 230 mg/dL and serum triglyceride level greater than 160 mg/dL were considered abnormal.

According to the ISKDC recommendation, prednisolone was started at a dose of 2 mg/kg/d (maximum, 60 mg/d to 80 mg/d) for 4 weeks, switched to alternative treatment and tapered as 10 mg/m^2 every 2 weeks. Continuation of oral steroid treatment to 8 weeks or 3 methyl-prednisolone pulses (in recently diagnosed patients) was recommended in steroid unresponsive patients. Remission was defined as zero-trace urine albumin in 3 consecutive days, resolution of edema, and serum albumin level higher than 2.5 g/dL. Steroid resistance was defined as persistent (2+ or more) proteinuria after 8 weeks of steroid treatment or 1 week poststeroid pulses.

Statistical Analyses

For the comparison of contingency tables, the chi-squared test was used, and in the case of expected numbers less than 5, the Fisher exact test was applied. Comparison of continuous variables was done using the *t* test. The statistical significance level was defined as a *P* value less than .05. All statistical analyses were performed with Stata (version 12.0, StataCorp LP, College Station, TX, USA).

RESULTS

A total of 238 children were included in this study, divided into group A (119 children treated between1991 and 2002) and group B (119 children treated in the second period between 2005 and 2012). The mean age at diagnosis of the patients was 67.0 months (range, 9 months to 14 years), and 58.6 years (range, 5 months to 14 years) in groups A and B, respectively (*P* = .08). Male-female ratio was 1.59 in group A and 1.38 in group B (*P* = .60). There was no significant difference in the serum levels of cholesterol, triglyceride, protein, and albumin and neither in 24-hour urine protein between the two groups. The frequency of hypertension and decreased kidney function between were comparable between the two groups. Microscopic hematuria was significantly less frequent in the recently examined patients (*P* = .02). Table 1 summarizes the symptoms and laboratory findings of INS in the two groups.

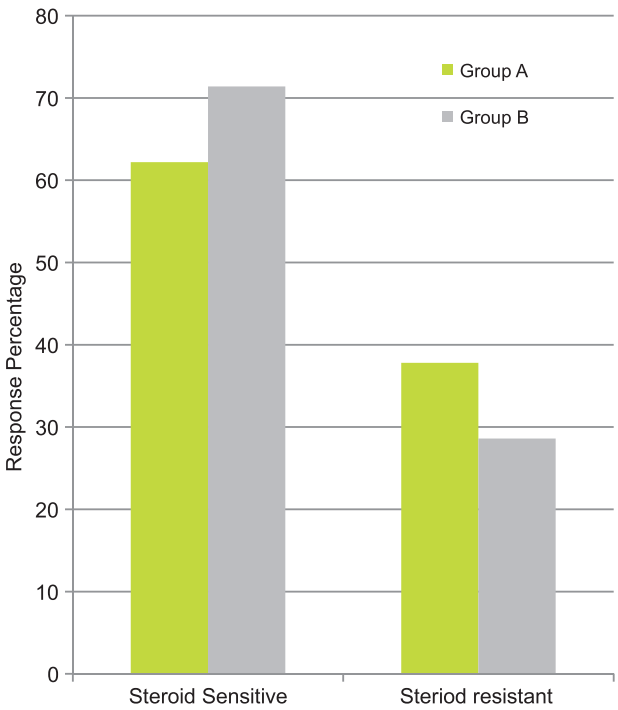
Overall, the initial response to corticosteroid therapy was 66.8%. Steroid responsiveness was insignificantly more frequent in group B (85 of 119 patients) in comparison with group A (74 of 119 patients, *P* = .13; Figure). Pathologic examination results were available in 45 patients in group A and 26 patients in group B; there was an insignificant increase in incidence of FSGS, and a decrease in both MCD and DMH in the latter group (Table 2). In the subgroup of patients with steroid resistance, kidney biopsy had been performed in 35 patients in group A and 17 patients in group B. Similarly, there was an insignificant increase in the incidence of FSGS (*P* = .09) and a corresponding decrease in both MCD (*P* = .17) and DMH in this population (*P* = .74).

Table 1. Clinical and Laboratory Findings in 238 Children With Idiopathic Nephrotic Syndrome

Parameters	Group A (n = 119)	Group B (n = 119)	*P*
Age at diagnosis, mo	67.02 ± 36.84	58.64 ± 36.48	.08
Male-female ratio	1.59	1.38	.60
Serum creatinine, mg/dL	0.64 ± 0.24	0.59 ± 0.39	.35
Serum protein, mg/dL	4.50 ± 0.71	4.23 ± 0.68	.10
Serum albumin, mg/dL	2.15 ± 0.55	2.19 ± 0.43	.62
Serum sodium, mg/dL	133.49 ± 15.42	136.18 ± 13.65	.16
Serum cholesterol, mg/dL	427.50 ± 133.70	408.15 ± 115.96	.28
Serum triglyceride, mg/dL	386.77 ± 167.73	355.64 ± 177.26	.21
24-hour urine protein, g/d	4.10 ± 3.53	3.32 ± 3.56	.12
Microscopic hematuria, %	50.0	34.6	.02
Hypertension, %	9.2	8.8	.93
Renal failure, %	7.8	7.6	.94

Table 2. Pathologic Findings in 71 Children with Idiopathic Nephrotic Syndrome

Pathology	Group A (%) (n = 45)	Group B (%) (n = 26)	*P*
Minimal change disease	15 (33.3)	7 (26.9)	.57
Diffuse mesengial hyperplasia	18 (40.0)	7 (26.9)	.26
Focal segmental glomerulosclerosis	12 (26.7)	12 (46.1)	.09



Response to corticosteroid treatment in 238 children with idiopathic nephrotic syndrome

DISCUSSION

We could not find an increasing trend in the incidence of steroid resistance in children with INS. This finding contradicts the observations published in recent years. Kim and colleagues, in a study on children with primary nephrotic syndrome admitted over the period 1994 to 2003 to two major centers in New Orleans, demonstrated a tendency towards increasing rates of steroid resistance in childhood nephrotic syndrome, compared with the results of ISKDC report.[6] Similarly, Banaszak and Banaszak showed a significant rise in steroid resistance in a study on 178 Caucasian children with new-onset nephrotic syndrome admitted to a pediatric hospital in southern Poland, from 15.8% in patients admitted during 1986 to 1995 to 31.4% during 1996 to 2005.[7]

Owing to the significant impact of race and geographic distribution of patients on clinical behavior of INS,[8-11] comparing the results of this study with those in other ethnicities might not be appropriate. Therefore, we tried to compare our result with previous studies published in Iranian children. The initial response to corticosteroids varied between 75.2% and 87% in recent years in Iran, which was in agreement with steroid response rate in Group B of the present study. Mortazavi and colleagues reported 75.2% response to steroids from northwestern Iran from 1999 to 2010.[3] Madani and coworkers reported steroid response in 81.5% of 238 children with INS treated during 1995-2007.[12] Ali and colleagues found 87% steroid sensitivity

between 1997 and 2004.[13] One of the earliest reports belonged to 1986; Bodaghi and colleagues reported a series of 310 children with primary nephrotic syndrome.[14] Interestingly, they found that only 53.8% of children were corticosteroid responsive, with the highest success rates among patients with MCD. We conclude that according to both the results of our study and comparison with earlier studies in our population, the incidence of steroid resistance might be decreasing.

Numerous recent studies suggest that the relative frequency of FSGS is increasing as compared to that of MCD.[8,10,15-19] In a prospective study carried out in India, a greater than two-fold increase in frequency of FSGS was observed between periods of 1990 to 1992 and 1992 to 1996.[17] Likewise, in another study from the United States, a two-fold rise in incidence of FSGS was reported (form 23% to 47%).[8] We observed that almost half of the patients who underwent kidney biopsy in the second period had FSGS, a finding which might indicate a rising incidence of this histopathology even in our population. Because having renal biopsy was not a necessary criterion for inclusion in this study, we cannot make a definitive statement about the overall frequency of FSGS and relation between renal pathology with steroid response pattern.

The incidence of hematuria has been reported to be higher in patients with steroid resistance.[3,20] Gulati and colleagues showed that children with non-MCD nephrotic syndrome had a significantly greater prevalence of microscopic hematuria as compared to those with MCD.[21] In Banaszak and Banaszak's study, it was observed that the frequency of patients with microscopic hematuria significantly increased in the later decade, concurrent with rises in steroid resistance frequency.[7] We found a significant decrease in the incidence of microscopic hematuria in this study, a finding that could be attributed to decreased incidence of steroid resistance.

CONCLUSIONS

According to the findings of this study, a trend towards increased frequency of steroid resistance is still questionable in this ethnically homogeneous population. Indeed, our findings are suggestive of a slight decrease in steroid resistance. Further studies with similar design are suggested in other ethnic populations.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Asinobi AO, Gbadegesin RA, Ogunkunle OO. Increased steroid responsiveness of young children with nephrotic syndrome in Nigeria. Ann Trop Paediatr . 2005;25:199-203.
2. Gipson DS, Massengill SF, Yao L, et al. Management of childhood onset nephrotic syndrome. Pediatrics. 2009;124:747-57.
3. Mortazavi F, Khiavi YS. Steroid response pattern and outcome of pediatric idiopathic nephrotic syndrome: a single-center experience in northwest Iran. Ther Clin Risk Manag. 2011;7:167-71.
4. [No authors listed]. Nephrotic syndrome in children: prediction of histopathology from clinical and laboratory characteristics at time of diagnosis. A report of the International Study of Kidney Disease in Children. Kidney Int. 1978;13:159-65.
5. Chesney R. The changing face of childhood nephrotic syndrome. Kidney Int. 2004;66:1294-302.
6. Kim JS, Bellew CA, Silverstein DM, Aviles DH, Boineau FG, Vehaskari VM. High incidence of initial and late steroid resistance in childhood nephrotic syndrome. Kidney Int. 2005;68:1275-81.
7. Banaszak B, Banaszak P. The increasing incidence of initial steroid resistance in childhood nephrotic syndrome. Pediatr Nephrol. 2012;27:927-32.
8. Bonilla-Felix M, Parra C, Dajani T, et al. Changing patterns in the histopathology of idiopathic nephrotic syndrome in children. Kidney Int. 1999;55:1885-90.
9. Feehally J, Kendell NP, Swift PG, et al. High incidence of minimal change nephrotic syndrome in Asians. Arch Dis Child. 1985;60:1018-20.
10. Srivastava T, Simon SD, Alon US. High incidence of focal segmental glomerulosclerosis in nephrotic syndrome of childhood. Pediatr Nephrol. 1999;13:13-8.
11. Bircan Z, Yavuz Yilmaz A, Katar S, Vitrinel A, Yildirim M.. Childhood idiopathic nephrotic syndrome in Turkey. Pediatr Int. 2002;44:608-11.
12. Madani A, Fahimi D, Taghaodi R, et al. An estimation of steroid responsiveness of idiopathic nephrotic syndrome in Iranian children. Iran J Pediatr. 2010;20:199-205.
13. Ali A, Ali D, Mehran H, Ali Z. Idiopathic nephrotic syndrome in Iranian children. Indian Pediatr. 2008;45:52-3.
14. Bodaghi E, Vazirian S, Madani A, Shmsa AM, Afzali HM, Elmi F. Primary nephrotic syndrome in Iran: clinicopathological study of 310 cases. Int J Pediatr Nephrol. 1986;7:127-30.
15. Korbet SM, Genchi RM, Borok RZ, et al. The racial prevalence of glomerular lesions in nephrotic adults. Am J Kidney Dis. 1996;27:647-51.
16. Braden GL, Mulhern JG, O'Shea MH, Nash SV, Ucci AA Jr, Germain MJ. Changing incidence of glomerular diseases in adults. Am J Kidney Dis. 2000;35:878-83.

17. Gulati S, Sharma AP, Sharma RK, et al. Changing trends of histopathology in childhood nephrotic syndrome. Am J Kidney Dis. 1999;34:646-50.
18. Dragovic D, Rosenstock JL, Panagopoulos G, et al. Increasing incidence of focal segmental glomerulosclerosis and an examination of demographic patterns. Clin Nephrol. 2005;63:1-7.
19. Borges FF, Shiraichi L, da Silva MP, Nishimoto EI, Nogueira PC. Is focal segmental glomerulosclerosis increasing in patients with nephrotic syndrome? Pediatr Nephrol. 2007;22:1309-13.
20. Davutoglu M, Ece A, Bilici M, et al. Steroid responsiveness of children with idiopathic nephrotic syndrome in southeastern region of Turkey. Ren Fail. 2007;29:855-9.
21. Gulati S, Sengupta D, Sharma RK, et al. Steroid resistant nephrotic syndrome: role of histopathology. Indian Pediatr. 2006;43:55-60.

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