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Histopathologic Characteristics of Steroid-Resistant Nephrotic Syndrome in Children in Iran

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Introduction: Nephrotic syndrome is the most common chronic renal disease in children. Mostly, it is controlled by steroids. Many underlying pathologies exist in patients with steroid-resistant nephrotic syndrome (SRNS). Among them are 'focal segmental glomerulosclerosis (FSGS) and 'minimal change disease' (MCD). Examining patients' clinicopathologic characteristics can be helpful by giving an insight into the etiology of steroid resistance and determining patient prognosis.

Material and Methods: This cross-sectional study was performed in 'Children's Medical Center' between 2001 and 2011. From 150 patients biopsied, seventy-one children with SRNS, aged 1-14 years, were included.

Results: Among 150 patients biopsied, 71 children (47.3%) had steroid-resistant nephrotic syndrome. Forty-four (62%) of these were boys. Upon pathologic investigation of SRNS cases, FSGS came in first, with the highest prevalence at a rate of 32.4%, and MGN came in last, at a rate of 5.6%. The mean age of disease onset was 4.7 years and the mean age of undergoing biopsy was six years.

Conclusions: In this study, the predominant pathologic pattern of steroid-resistant nephrotic syndrome was FSGS, a finding similar to that of most studies conducted in this field. MCD was observed in 21.1% of patients, which indicates the variety in reporting renal lesions, particularly, regarding the diagnoses of MCD, mesangio-proliferative glomerulonephritis and early stages of FSGS.

Keywords: Steroid-resistant; Nephrotic syndrome; Child.

Running Title: Histopathologic Characteristics of Steroid-Resistant Nephrotic Syndrome

Introduction

Nephrotic syndrome, which is a common complication of glomerular diseases in children, includes massive proteinuria, hypoalbuminemia, edema and hyperlipidemia [1]. Idiopathic Nephrotic Syndrome affects 1 to 3 of every 10000 children under 15 years of age and although most cases respond to steroid therapy, 20% are classified as steroid-resistant [2]. This rate varies across different studies from 10% to 20% [3].

Moreover, children with steroid-resistant nephrotic syndrome (SRNS) may have different histopathologies [2]. SRNS is a challenge to pediatric nephrologists and its histopathologic diagnosis helps predict response-to-treatment and course of disease, also it is associated with a higher risk of becoming a chronic renal disease [4].

Children with SRNS and FSGS or MCD pathologies

are probably more resistant to immunosuppressive drugs. Hence, the treatment regimen will differ once the type of pathology is known [5].

SRNS children with MCD have a greater chance of remission compared to those with a non-MCD pathology and have better long-term prognosis. Therefore, biopsy plays an important role in the prognosis of children with SRNS [6].

Currently, and to our knowledge, fewer histopathologic studies have been conducted on SRNS in Iran as a result of limited biopsy facilities for pediatric renal diseases. Hence, the goal of this study was to examine these characteristics in children attending Children’s Medical Center.

Materials and Methods

According to previous studies, the prevalence of resistant nephritic syndrome is about 10% [3,19]. Therefore, with a=0.05 and d=0.05, the sample size was calculated as 139. Finally, 150 patients entered the study. Among them 71 children had SRNS.

A cross-sectional study was conducted on 71 children with SRNS aged 1 – 14 years. These children were attending Tehran’s *Children’s Medical Center* between 2001 and 2011 and had undergone histopathologic examinations.

Inclusion criteria: 1) Age of onset of disease < 15 years; 2) Having idiopathic nephrotic syndrome (Idiopathic refers to nephritic syndrome with unknown origin) (5) along with the following indicators at the time of diagnosis:

severe proteinuria (>40mg/square meter of body surface area/hour),

hypoalbuminemia (serum albumin < 2.5mg/dL);

3) non-response to treatment (lack of remission) or resistance to treatment, i.e. no remission after 4 weeks of treatment with a daily dose of 60mg/squaremeter of body surface area

prednisolone and 3 intravenous pulse doses of methyl-prednisolone afterwards, or no remission after four weeks of treatment with steroid followed by alternate-day prednisolone for another four weeks [19]. Exclusion criteria were secondary nephrotic syndrome (following lymphoma, systemic lupus erythematosus, diabetes mellitus, various viral infections such as hepatitis etc.).

Data was extracted from patients’ recorded files. If need, they were contacted via phone or spoken to in person. The gathered data entered data collection tool and analyzed using SPSS software [version 13].

Results

Among 150 patients with idiopathic nephrotic syndrome biopsied for various reasons, 71 had SRNS. Forty-four (62%) were boys and 27 (38%) girls.

The mean age of participants at the start of study was 4.7±3.1 years. Their mean age at the time of biopsy was 6.9±3.35 years. The gap between the onset of disease and biopsy was 0 to 10 years (mean=2.2 years). Pathologic examination revealed FSGS at a rate of 32.4% and Diffuse Mesangio-Proliferative GN(DMP) at a rate of 28.2%. The male:female ratio was 1:1 for membranous GN(MGN) (table 1). Clinical and lab findings were as follows: edema (94.4%), hyperlipidemia (29.6%), microscopic hematuria (49.3%) and hypertension (38%). None of them had macroscopic hematuria.

Table 1. Characteristics of patients with SRNS according to histopathologic subtypes

	Fr* % (n=71)	Age of onset of disease	Age of biopsy	Interval	M/F**
MGN	5.6	1.6(0.8)§	3.8(1.5)	2.1(0.9)	1
MPGN	12.7	8.6(3.7)	10(3.6)	1.4(0.7)	1.25
FSGS	32.4	5.7(2.8)	7.7(2.8)	2(2.2)	1.56
DMP	28.2	3.8(2.5)	5.5(2.6)	1.7(1.7)	1.88
MCD	21.1	3.1(1.7)	6.8(3.8)	3.7(3.4)	2.04

MGN: membranous GN, MPGN: mesangiocapillary or membranoproliferative GN, FSGS:focal segmental glomerulosclerosis, DMP:diffuse mesangio proliferative GN, MCD:minimal change disease, *frequency **male to female ratio §:mean(SD)

Discussion

According to our findings, the most common pathology in steroid-resistant nephrotic syndrome was FSGS (32.4%), consistent with those of other studies [1, 3, 6-9]. Based on the biopsy results of some studies, more than a half of NS cases without response to steroids had FSGS [1]. Table 2 illustrates a comparison between the frequencies of various histopathologic types of SRNS. In a study conducted by Kim et al. in the USA, the most common pathologies found in SRNS were FSGS, followed by MCD [7]. However in Kuwait, Alrashid et al. found the highest frequency for MCD and in

another study conducted in Nigeria, MPGN was the most prevalent one [10, 11]. Also In India, the most frequent type of SRNS was MCD [12].

In our study, the highest frequencies belonged to FSGS and DMP, respectively. Our findings were similar to those of Ahmadzadeh et al's study in

Ahwaz (a city in Iran) [8]. The frequency percent of DMP, however, was higher in our study than all the others [3, 4, 6, 8, 11]. Safaei&Madani found FSGS as the most common pathology in SRNS [13, 14].

Table 2. Comparison of histopathologic distribution of SRNS in different studies

	Mubarak et al (3)	Olowu et al (11).	Kari et al. (4)	Gulati et al (6)	Alrashid et al (10)	Seif et al (18)	Gargah et al (9)	Pradhan et al (12)	Ahmadzadeh et al (8)	Our study
MGN	8.2	4.3		1.4		9.4		5		5.6
MPGN	4.8	43.5		1.6		7.5		2.5	15.3	12.7
FSGS	38.7	39.1	39	58.8	15	30.2	50	30	34.6	32.4
DMP	10.2	8.7	17	17.6		1.9	20		19.2	28.2
MCD	23.1	4.3	8	17.6	65	24.5	30	45	15.3	21.1

MGN: membranous GN, MPGN: mesangiocapillary or membranoproliferative GN, FSGS: focal segmental glomerulosclerosis, DMP:diffuse mesangio proliferative GN, MCD:minimal change disease

The differences observed between the frequencies of SRNS histopathologic subtypes in different studies may be attributed to ethnic, environmental and genetic differences. Furthermore, different definitions for the inclusion criteria and indications for biopsy could explain this difference. In addition, early FSGS lesions or early FSGS may not be detected in initial pathologic examinations [3, 15].

Earlier studies have shown the significant effect of ethnic and geographical factors in steroid response and histopathologic types of idiopathic nephrotic syndrome [16]. Moreover, according to various studies, SRNS patients whose renal biopsies indicated MCD in the earlier stages of disease later developed FSGS. So we may conclude that both lesions are natural progressions of the same process [17].

The male sex was predominant in all pathologic subtypes except for MGN. The highest ratio of boys to girls was seen in patients with MCD. Gulati et al. found this proportion higher in boys, but, unlike our findings, found the highest ratio in MGN [6]. Among various pathologic diagnoses, the highest mean age at the time of onset of disease and the highest mean age at biopsy were observed in MPGN. Moreover, the shortest time gap between disease onset and biopsy was observed in the same subtype.

Age of disease onset is important, because the higher the age of child when he or she is affected, the higher the chance of acquiring SRNS and FSGS [7].

Conclusion

In the current study, the most common pathologic pattern of steroid-resistant nephrotic syndrome was FSGS, similar to most studies conducted in this field. Examining histopathologic characteristics of patients around the world can significantly help identify the reasons behind steroid resistance. Furthermore, comparing these pathologic findings can help explain the roles of environmental and generic factors to some extent.

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Conflict of Interest

Authors have no conflict of interest to declare.

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