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Predictive Parameters of Steroid Dependency in Minimal Change Disease

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Abstract

The most common type of nephrotic syndrome in children is minimal change disease (MCD), which is usually responsive to steroid therapy. Steroid dependency is one of the handicaps in the management of these children. Thus, the early prediction of the disease course may improve treatment strategy. Demographic characteristics and laboratory parameters of 35 patients at the time of MCD diagnosis were retrospectively obtained from the hospital records. There were 23 (65%) patients with steroid sensitive (SSNS) and 12 (35%) with steroid dependent nephrotic syndrome (SDNS). There was a significant difference between the patients with SSNS and SDNS in terms of age at diagnosis, remission time, and mean values of platelet volume, low density lipoprotein cholesterol, uric acid, urine protein-to-creatinine ratio, total cholesterol and creatinine ($p=0.003$, $p<0.001$, $p=0.013$, $p=0.006$, $p=0.036$, $p=0.02$, $p=0.003$, and $p=0.034$, respectively). The prediction of early markers of steroid dependency can reduce the side effects of steroids and facilitate the use of appropriate drugs.

Keywords: Children, minimal change disease, nephrotic syndrome, steroid dependency

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Introduction

Nephrotic syndrome (NS) is the most frequent pediatric glomerulopathy characterized by proteinuria, hypoalbuminemia, and edema.[1] The most common type of childhood NS is minimal change disease (MCD)accounting for up to 90% of cases.[2] As the main treatment of MCD is immunosuppression with corticosteroids, immune system dysregulation strongly indicates a pathogenic role in disease development.[3,4] MCD generally responds well to corticosteroids, although 50-75% of patients, especially those aged <5 years, experience frequent disease relapses and half of the frequent relapsers eventually become steroid-dependent during steroid tapering or after discontinuation.[3-6] Patients with frequently relapsing NS (FRNS) or steroid-dependent NS (SDNS) are at a major risk of developing complications related to the prolonged use of steroids.[6,7] Thus, this study aimed to verify the predictive factors for NS attacks in pediatric patients with MCD.

Highlights

- It is important to predict the risk factors for steroid dependency in nephrotic syndrome.
- Age at diagnosis, remission time, mean platelet volume, total and low density cholesterol, uric acid, creatinine, and proteinuria levels can be used as the predictive markers of steroid dependency in nephrotic syndrome.

Material and Method

The study included 35 patients (23 male, 12 female) diagnosed with steroid-responsive MCD and 35 healthy children (16 male, 19 female) as the control group. After the ethical approval was obtained from Manisa Celal Bayar University ethic committee) (29.12.2021, Decision No:20.478.486/1119), the demographic characteristics and laboratory parameters of the patients at the time of MCD diagnosis were retrospectively conducted from the patients' files and hospital records. The children were separated into two groups based on their steroid response as steroid-sensitive NS (SSNS) and SDNS. SSNS was defined as on response to 60 mg/m2 corticosteroid per day within four to six weeks, SDNS as two consecutive attacks during corticosteroid treatment or within 14 days of its cessation, and FRNS as ≥2 relapses per six months or ≥4 relapses per year.[2,8] Hemoglobin levels, leukocyte, lymphocyte, neutrophil, monocyte and platelet counts, platelet indices [mean platelet volume (MPV), platelet distribution width (PDW), and plateletcrit (PCT)], red cell distribution width (RDW), C-reactive protein (CRP), lipid profile [LDL (low-density lipoproteins) cholesterol, HDL (high-density lipoproteins) cholesterol, triglycerides (TG), total cholesterol], albumin, creatinine, urea, and uric acid levels were recorded at the time of the patients' first diagnosis. The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), which is considered to be parameters for predicting severity and prognosis of many inflammatory diseases, including kidney disease [9-12], were calculated using the complete blood counts. Nephrotic range proteinuria was determined as urine protein/creatinine ratio of >2 mg/mg. Patients with any inflammatory, immunologic or other chronic illness (hyperthyroidism, hypertension, obesity, vitamin D deficiency, obesity) those taking medication other than steroids, and those resistant to steroids were excluded. There were no patients with kidney disease.

Statistical analysis

Statistical analysis was achieved using the SPSS version 22.0. Continuous parameters were detected as mean±standard deviation and qualitative data as frequencies and percentages. The normality of the distribution of data was evaluated with graphical methods, and the Kolmogorov-Smirnov or Shapiro-Wilk test. The chi-square test was performed to compare qualitative parameters while Student's t-test or the Mann-Whitney U test was utilized to analyze the differences in continuous variables. A p value of <0.05 was determined as significant.

Results

The demographic characteristics and laboratory data of the children with MCD and the control group are presented in **Table 1**. The mean age of the patients with MCD was 5.2±1.8 years, and 66% were male. The platelet counts were significantly higher and MPV level were lower in patients with MCD than the controls (p=0.002 and p=0.02, respectively. No significant difference was detected among the two groups in terms of age, gender, hemoglobin level, leukocyte count and uric acid levels (p=0.27, p=0.09, p=0.77, p=0.69, and p=0.17, respectively).

Table 1.
Demographic and laboratory parameters of the patient with MCD and control groups

	Patient	Control	p value
Age at diagnosis	5.2±1.8	5.6±2.8	0.27
Gender (male/female)	23/12	16/19	0.09
Hemoglobin (g/dL)	12.8±1.6	12.7±1.5	0.77
Platelet (103/µL)	418 ±150	328±69	0.002
MPV (fL)	7.9±1.2	8.5±1	0.02
WBC (103/µL)	9.8±2.5	10±2.5	0.69
Uric acid (mg/dL)	4.5±1.1	4.3±1	0.17

Abbreviations: MCD: minimal change disease, MPV: mean platelet volume, WBC: white blood cell

There were 23 (65%) children with SSNS and 12 (35%) children with SDNS (**Table 2**). All the patients with SDNS had frequent relapses. Five patients of the SSNS group were frequent relapsers. Sixteen patients with SSNS (70%) and 11 with SDNS (92%) had relapses associated with concomitant upper respiratory tract (URT) infections although the difference between these groups was not significant (p=0.27). There was a significant difference among these two groups in terms of age at diagnosis, remission time, and MPV, LDL, uric acid, urine protein-to-creatinine ratio, cholesterol and creatinine levels (p=0.003, p < 0.001, p=0.013, p=0.006, p=0.036, p=0.02, p=0.003, and p=0.034, respectively) (Table II). There was no significant difference in gender, hemoglobin, leukocyte, platelet, PCT, PDW, RDW, neutrophil, lymphocyte, NLR, PLR, monocyte, albumin, TG, HDL, CRP, and urea between the SSNS and SDNS groups (p=0.5, p=0.8, p=0.8, p=0.7, p=0.7, p=0.6, p=0.9,

p=0.8, p=0.65, p=0.38, p=0.5, p=0.2, p=0.6, p=0.4, p=0.2, and p=0.3, respectively) (**Table 2**). MPV counts at the time of initiation of steroid therapy remained low, while they normalized after steroid response and during remission.

Table 2.
Comparison of demographic and laboratory parameters of the patients according to steroid response

	SSNS (n=23)	SDNS (n=12)	p value
Age at diagnosis	5.8±2	4±0.7	0.003
Gender (M/F)	16/7	7/5	0.5
Remission time (day)	5.4±1.4	12±1.7	<0.001
Attack number	2.5±1.6	8.5±3.7	0.006
Hemoglobin (g/dL)	12.7±1.6	12.9±1.7	0.8
WBC (103/µL)	9.8±2.6	10±2.3	0.8
PLT (103/µL)	425±161	404±133	0.7
PCT (%)	0.34±0.1	0.32±0.1	0.7
PDW (fL)	16±0.6	16±0.7	0.8
MPV (fL)	8.4±1.2	7.5±0.8	0.013
RDW (%)	14.4±1.9	13.8±1	0.6
Neutrophil (103/µL)	4.8±1.8	5±2.4	0.9
Lymphocyte (103/µL)	3.9±2	4±1.3	0.8
NLR	1.7±1.2	1.5±1.1	0.65
PLR	131±60	111±59	0.38
Monocyte (103/µL)	615±212	691±407	0.5
Albumin (g/dL)	1.7±0.3	2±1	0.2
TG (mg/dL)	215±76	206±66	0.6
Total cholesterol (mg/dL)	412±88	311±103	0.003
LDL (mg/dL)	300±78	209±104	0.006
HDL (mg/dL)	77.7±20	72±19	0.4
Uric acid (mg/dL)	4.2±1	5±1	0.036
CRP (mg/dL)	0.7±1.4	0.3±0.3	0.2
Urea (mg/dL)	27±13.5	27±26	0.3
Creatinine (mg/dL)	0.3±0.2	0.4±0.1	0.034
Urine Pr/Cr (mg/mg)	6.5±1	11±1.5	0.02

Abbreviations: SSNS: steroid-sensitive nephrotic syndrome, SDNS: steroid-dependent nephrotic syndrome, F: female, M: male, WBC: white blood cell, CRP: C-reactive protein, MPV: mean platelet volume, PCT: plateletcrit, PDW: platelet distribution width, PLR: platelet-to-lymphocyte ratio, NLR: neutrophil-to-lymphocyte ratio, RDW: red cell width distribution, Pr/Cr: protein-to-creatinine ratio)

Discussion

Nephrotic syndrome is the most common childhood chronic glomerular disease.[1,2] Steroid dependency is one of the major difficulties in the treatment of patients with NS. The long-term steroid administration in patients with SDNS can cause complications such as diabetes, hypertension, obesity, osteoporosis, short stature, susceptibility to infections, gastritis, and posterior subcapsular cataracts, and therefore the use of alternative immunosuppressant agents is necessary in these patients.[6,7] Although, the pathogenesis of nephrotic syndrome remains uncertain, the role of the immune system and inflammation is reported in many studies.[3,4,13] Inflammatory mediators, such as neutrophils, lymphocytes, platelet, and platelet indices have been shown to be activated in NS.[14-17] The early prediction of patients with SDNS using these inflammatory parameters or other biochemical markers will therefore be useful to closely monitor these patients. This report aimed to find out the demographic characteristics and laboratory markers to predict steroid dependency in patients with NS.

In the current research, the mean age of the patients at the onset of MCD was 5.2±1.8 years, consistent with previous reports.[18,19] There was 2:1 male dominancy in the MCD group, which is also in agreement with the literature.[2,5] The patients in the SDNS group were found to be younger at the onset of the disease, similar to the research of Andersen et al.[20] Conversely, Kabuki et al. have reported an increase of steroid dependency with age.[21] It was reported that males were more at risk of developing steroid dependency than females.[20] This may be a result of the predominance of male patients with NS. However, we found no significant difference in steroid dependency between males and females in the current study.

Most SDNS cases in the current study had relapses after URT infections. Similarly, Yap et al.[6] and Abdel-Hafez et al.[22] reported that patients who did not have any attack during URT infection might be less likely to be steroid-dependent, although this was not statistically significant.

Platelets and platelet indices were found to be related to the inflammatory process of NS in previous studies.[15-17,23] Previous studies detected thrombocytosis at the diagnosis of MCD[23], similar to the current study. It is assumed that hypoalbuminemia and hypercholesterolemia that occur in NS lead to platelet aggregation and are responsible for thrombocytosis as it is presented a negative correlation between albumin and PLT in the current study. However, Mittal et al. reported normal PLTcounts in children with NS.[24] Although, Kocyiğit et al.[17] and Gulleroglu et al.[15] reported higher MPV in patients with MCD, in the current study, MPV was determined to be lower in the MCD group than in the control group, supporting the results presented by Wasilewska et al.[16] Gulleroglu et al.[15] detected lower MPV levels in steroid-resistant NS. In the current study, steroid dependency was observed to be correlated with decreased MPV levels but did not have any correlation with platelet levels.

NLR and PLR are used as inflammatory indices for the prognostic prediction of autoinflammatory diseases.[9-12] However, in the recent search, we found no association between these parameters and steroid dependency in MCD. Jamee et al. reported NLR and PLR not suitable for predicting steroid response in their patients with childhood NS.[25] However, they included steroid sensitive and resistance patients with NS, not only MCD patients to their study.

This study showed that uric acid levels were associated with steroid dependency in MCD. Song et al.[26] revealed hyperuricemia as an independent risk factor for progression to end stage kidney disease in children with MCD. Asakawa et al.[27] reported that hyperuricemia was related to podocyte injury and proteinuria. MCD is also known as a podocytopathy, and there may be an association between podocyte damage in SDNS and hyperuricemia. The rate of proteinuria was also detected to be statistically higher in the SDNS group in our study. Proteinuria and hyperuricemia may cause steroid dependency through podocyte injury.

The limitations of the recent research are that the retrospective nature and the small sample size, which may limit the generalization of results.

Conclusion

It is important to predict the risk factors for steroid dependency in NS in order to plan long-term management and avoid complications related to steroid use. Age at diagnosis, remission time, MPV, total and LDL cholesterol, uric acid, creatinine, and proteinuria can be used as the predictive markers of steroid dependency in NS. Future large-scale and multicenter studies are needed to corroborate our findings.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

Conflict of Interest: There are no conflicts of interest in connection with this paper, and the material described is not under publication or consideration for publication elsewhere.

Ethics Committee Approval: The study was carried out with the permission of Manisa Celal Bayar University Clinical Researches Ethics Committee (Date: 29.12.2021, Decision No:20.478.486/1119).

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Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

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