Observational Study on Serum Lipid Profile Derangement in Pediatric Nephrotic Syndrome Patients

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Abstract: Background: Nephrotic syndrome is primarily a paediatric disorder and is 15 times more common in children than adults.

Aims and Objectives: To study the derangement of serum lipid profile in children 2 to 12 years with nephrotic syndrome

Subject and methods: The present study was a prospective observational pilot study on children with NS from Nephrology Unit of Mansoura University Children's Hospital (MUCH) over the years 2022 & 2023. The study included Nephrotic syndrome (NS) patients submitted to glucocorticosteroid treatment as a first line therapy. Lipid Profile was measured. our results we concluded that nephrotic syndrome had generalised hyperlipidemia and abnormal lipid profile occur mostly among cases with SRNS.

1.Introduction

Nephrotic syndrome (NS) is one of the most common pediatric glomerular disorders with substantial morbidity worldwide, especially in developing countries. NS is relatively a rare condition, which can occur in patients of any age with its incidence of three patients per 100,000 patients per year [1]. Incidence of NS has remained stable over the past 60 years [2]. NS is characterized by generalized edema, massive proteinuria, hypoalbuminemia, and hyperlipidemia. It involves podocyte damage with tubulointerstitial fibrosis and glomerulosclerosis. NS may be acquired or congenital; the acquired causes may either be primary (idiopathic) or secondary that can originate due to diverse secondary causes or because of genetic causes [3].

Idiopathic nephrotic syndrome (INS) is the most frequent primary glomerular disease in the pediatric population, approximately 90% of children with NS have INS [4]. The onset of the disease occurs usually between the ages of 2 and 8 years, with a peak of incidence between 3 and 5 years [5]. The physio-pathologic mechanisms of INS have not been completely

clarified; however, the disease is triggered by an increase in glomerular permeability caused by an abnormal immunologic response, that results in an alteration of the capillary structure and of the integrity of the glomerular membrane [6].

NS necessitates chronic treatment with steroids or other immunosuppressants, angiotensin converting enzyme inhibitors and monoclonal antibodies as there are no specific targeted treatments available so far [7]. Following which, with the help of biopsy, the therapies are further directed with other immunosuppressive agents and management with ACE inhibitors or ARBs [8]

Children with steroid-sensitive nephrotic syndrome generally have a good prognosis regarding the maintenance of normal kidney function even in the case of frequent relapses. Based on response to steroids, SSNS is traditionally categorized into broad groups, with steroid SSNS representing 90% of children presenting with this condition. Approximately 25% of these children will be effectively cured and have no further relapses

after an initial course of steroids. The remainder go on to have relapsing disease and are characterized based on the pattern of relapses as infrequently relapsing, frequently relapsing (FR) or steroid dependent (SD). There is significant inter-individual variability in clinical course and treatment response that cannot be predicted based on demographics, relapse pattern, or previous treatment [9].

The aim of the present study was to study the derangement of serum lipid profile in children 2 to 12 years with nephrotic syndrome.

Patients and methods:

The present study was a prospective observational pilot study on children with NS from Nephrology Unit of Mansoura University Children's Hospital (MUCH) over the years 2022 & 2023.

The study included Nephrotic syndrome (NS) patients submitted to glucocorticosteroid treatment as a first line therapy. They are further assigned to subgroups upon their initial response to steroid treatment, according to the ISKDC definitions and guidelines: Steroid sensitive (SSNS): steroid sensitivity was defined as a complete remission within initial 4 weeks of treatment, primarily steroid sensitivity (PSS)—no relapses during initial 4 weeks of treatment. Steroid dependence (SDNS): 2 consecutive relapses during therapy or within 2 weeks after stopping steroid therapy. Frequently relapsing (FRNS): identified with ≥2 relapses in the initial six months of therapy or with ≥4 relapses in a period of one year. Steroid resistance—failure to achieve complete remission after 8 weeks of corticosteroid therapy. Heathy children of matched age and sex will be included in the study from the General Outpatient Clinic of MUCH.

Children with Congenital Ns, Diabetic patients, Leukemia and transplantation were excluded from our study.

All patients in the present study were subjected to history taking including age, sex, and residency. Clinical presentation, Date & age of onset of Nephrotic Syndrome, Previous Medical Conditions, Medications, Family History of Nephrotic Syndrome and Response to treatment Clinical Information specially Blood Pressure and Edema (location, severity, duration). Physical Examination including Weight, Height, BMI, Edema. Renal Biopsy, Abdominal Ultrasound or Renal Doppler Ultrasound, Magnetic Resonance Imaging (MRI), Computed Tomography (CT(Scan. Laboratory Information including Hemoglobin, Red blood cell count, White Blood Cell Count, Platelet Count, Serum Albumin, Creatinine, Albumin/creatinine ratio, Blood Urea Nitrogen, Total Cholesterol, Triglycerides, High-density Lipoprotein, Low-density Lipoprotein, Serum Calcium, Serum Phosphorus, Serum Potassium, Serum Sodium Urine analysis for (Protein-R.B. Cs-W.B. Cs)

Statistical Analysis:

The collected data was revised, coded, and tabulated using Statistical package for Social Science (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). Kolmogorov-Smirnov test was used to assess normality of data. Mean, standard deviation ($\pm$ SD), standard error ($\pm$ SE), median, and range were used for numerical data. Frequency and percentage were used for non-numerical data. Student T Test was used to assess the statistical significance of the difference between two study group means. Paired T Test was used to assess the statistical significance of the difference of a parametric variable between two times period. Mann Whitney Test (U test) was used to assess the statistical significance of the difference of a non-parametric variable between two study groups. Willcoxon Test (Z test) was used to assess the statistical significance of the difference of a non-parametric variable between two times period. The Kruskal Wallis test was used to assess the statistical significance of the difference between more than two study group nonparametric variables. Chi-Square test was used to examine the relationship between two qualitative variables. Fisher Exact or Monte Carlo test: was used to examine the relationship between two qualitative variables when the expected count is less than 5 in more than 20% of cells

Results:

The current study was conducted on 60 patients with NS. Their mean age was 9.2, ranged from 1.75 to 17.5 years. They were 56.7% males and 43.3% females. In addition to 43 healthy control subjects of matched age and gender (table 1).

Table 2 presents the family history and consanguinity degree among patients with nephrotic syndrome. Out of the 60 patients, 3.3% had a positive family history of nephrotic syndrome, while the majority (96.7%) had a negative family history. Regarding consanguinity degree, 13.3% of patients had a positive consanguinity degree, while 86.7% had a negative consanguinity degree.

The NS group had significantly higher levels of triglycerides ($p2<0.001$), cholesterol ($p2<0.001$), LDL ($p2<0.001$), HDL ($p2=0.001$) compared to the control group (table 3), at the onset of the disease.

No significant differences were found between SSNS, SDNS and SRNS regrading creatinine ($p>0.05$ for each) (table 4).

TC and LDL differed significantly between SSNS, SDNS, SRNS. These differences were attributed to significantly higher levels among SRNS when compared to SSNS. Otherwise, no significant differences were found regarding lipid profile at disease onset according to treatment outcome (table 5).

Table 1: Comparison between patients with nephrotic syndrome and control group regarding demographic data.

	NS patients N = 60		Control N = 34		Test	P
	No.	%	No.	%		
Sex						
Male	34	56.7	23	67.6	$X^2=1.096$	0.295
Female	26	43.3	11	32.4		
Age (years)						
Mean ± SD.	9.20 ± 3.93		10.28 ± 3.30		U=1209.5	0.135
Median	10.0		11.0			
Min. – Max.	1.75 – 17.50		3.0 – 15.0			
Residency						
Urban	1	1.7	0	0.0	$X^2=0.573$	FE 1.000
Rural	59	98.3	34	100.0		

SD.: Standard deviation, Min.: Minimum, Max.: Maximum, U: Mann Whiteny test,
X^2: Chi–Square, FE: Fisher Exact, p: Comparing NS and control group.

Table 2: Family history and consanguinity degree among patients with nephrotic syndrome.

	NS patients N = 60	
	No.	%
Family history		
Negative	58	96.7
Positive	2	3.3
Consanguinity degree		
Negative	52	86.7
Positive	8	13.3

Table 3: Lipid profile in nephrotic syndrome and control groups

	NS patients	Control N = 34	p1	p2	p3
	At onset of disease				
TG (mg/dL)	**N = 58**				
Mean ± SD.	253.8 ± 211.9	85.47 ± 34.57	U=74.5 p1<0.001*	U=109.0 p2<0.001*	Z=1.332 p3=0.183
Median	203.5	80.0			
Min. – Max.	22.0 – 1438.0	70.0 – 280.0			
Cholesterol(mg/dL)	**N = 58**				
Mean ± SD.	463.6 ± 121.3	135.1 ± 8.12	U=0.0* p1<0.001*	U=0.0* p2<0.001*	Z=4.340* p3<0.001*
Median	463.0	135.5			
Min. – Max.	255.0 – 740.0	113.0 – 150.0			
LDL (mg/dL)	**N = 57**				
Mean ± SD.	347.0 ± 122.1	69.42 ± 7.84	U=0.0* p1<0.001*	U=0.0* p2<0.001*	Z=3.267* p3=0.001*
Median	352.0	68.50			
Min. – Max.	96.0 – 646.0	51.0 – 85.0			
HDL (mg/dL)	**N = 58**				
Mean ± SD.	61.98 ± 22.59	49.82 ± 3.78	U=793.5 p1=0.119	U=575.0 p2=0.001*	Z=1.945 p3=0.052
Median	57.0	49.0			
Min. – Max.	29.0 – 130.0	45.0 – 60.0			

SD.: Standard deviation, Min.: Minimum, Max.: Maximum, U: Mann Whiteny test, Z: Willcoxon test.

P1: Comparing NS and control group at sampling,

P2: Comparing NS and control group at onset of disease,

P3: Comparing at sampling and at onset of disease in NS group,

*: Significant when p value <0.05.

Table 4: Correlation between treatment response and creatinine among patients with nephrotic syndrome.

Creatinine (mg/dL)	SSNS	SDNS	SRNS	Test	p
At sampling	**N = 7**	**N = 16**	**N = 36**		
Mean ± SD.	0.56 ± 0.32	0.48 ± 0.12	0.69 ± 0.79	H= 0.328	0.849
Median	0.50	0.45	0.50		
Min. – Max.	0.20 – 1.20	0.30 – 0.70	0.20 – 3.90		
At onset of disease	**N = 7**	**N = 16**	**N = 36**		
Mean ± SD.	0.46 ± 0.16	0.44 ± 0.12	0.61 ± 0.98	H= 0.184	0.912
Median	0.50	0.50	0.40		
Min. – Max.	0.20 – 0.60	0.30 – 0.60	0.20 – 6.20		

SD.: Standard deviation, Min.: Minimum, Max.: Maximum, H: Kruskal Wallis test.

P: Comparing the different treatment responses.

SD.: Standard deviation, Min.: Minimum, Max.: Maximum, H: Kruskal Wallis test,

P1: Comparing the different treatment responses, P2: Comparing SSNS and SDNS.

P3: Comparing SSNS and SRNS, P4: Comparing SDNS and SRNS.

: Significant when p value <0.05

Table 5: Relation between treatment response and lipid profile at onset of disease among patients with NS.

At onset of disease	SSNS	SDNS	SRNS	Test	p1	Pairwise
TG (mg/dL)	N = 7	N = 16	N = 35			
Mean ± SD.	373.3 ± 473.4	199.7 ± 128.4	254.6 ± 155.3	H= 3.377	0.185	–
Median	190.0	137.0	220.0			–
Min. – Max.	104.0 – 1438.0	114.0 – 480.0	22.0 – 695.0			–
Cholesterol (mg/dL)						
Mean ± SD.	364.4 ± 99.76	461.6 ± 146.8	484.3 ± 104.5	H= 6.671*	0.036*	p2=0.056
Median	320.0	468.5	496.0			p3=0.010*
Min. – Max.	260.0 – 563.0	265.0 – 740.0	255.0 – 685.0			p4=0.505
LDL (mg/dL)						
Mean ± SD.	236.6 ± 54.87	342.6 ± 162.7	371.7 ± 97.36	H= 7.980*	0.018*	p2=0.059
Median	213.0	365.0	383.5			p3=0.005*
Min. – Max.	170.0 – 309.0	96.0 – 646.0	176.0 – 550.0			p4=0.313
HDL (mg/dL)						
Mean ± SD.	60.0 ± 25.90	62.19 ± 17.48	62.29 ± 24.52	H= 0.564	0.754	–
Median	57.0	57.50	57.0			–
Min. – Max.	29.0 – 110.0	40.0 – 116.0	34.0 – 130.0			–

Discussion:

Nephrotic syndrome is primarily a paediatric disorder and is 15 times more common in children than adults. The incidence is 2-3/100,000 children per year; and the majority of affected children will have steroid-sensitive minimal change disease. The characteristic features of nephrotic syndrome are heavy proteinuria (>3.5 g/24 hr in adults or 40 mg/m2/hr in children), hypoalbuminemia (<2.5 g/dl), oedema, and hyperlipidemia (serum cholesterol >200mg/dl). Hyperlipidemia is recognised as a common finding in patients with nephrotic syndrome since 1917, when hypercholesterolemia was described as a feature of nephrotic syndrome [9].

The present study showed that mean age was 9.2 with male predominance in agreement with most previous studies as in Egypt [10], Iran [11] and New Zealand [12]. The childhood nephrotic syndrome has a male predominance [13, 14].

Family history and consanguinity degree among patients with nephrotic syndrome. Out of the 60 patients, 3.3% had a positive family history of nephrotic syndrome, while the majority (96.7%) had a negative family history. The incidence of positive family history was higher than in other studies (2% in Gulati et al **(Gulati, 1994 #9903).** Higher incidence was observed in Mattoo et al in a study done in Saudi Arabia, who reported a 6% positive family history [15]. This is probably due to the

same cultural background in Egypt and Saudi Arabia

Previous study found consanguinity 23.3%. In Turkey, the frequency of consanguineous marriage in patients with nephrotic syndrome

was identified as 18.3% in the study conducted in Istanbul [16] and as 15.2% in a study carried out by [17], while the frequency was determined as 25.9% in study by [18].

The mean disease duration was 3.71 years with a standard deviation of 3.02 years. The median duration was 3.0 years, ranging from a minimum of 0.10 years to a maximum of 11.0 years.

Regarding clinical symptoms, Puffy eye lids were observed in 1.7% of patients, while 6.7% had abdominal enlargement. The majority of patients experienced generalized edema (91.7%), ascites (5.0%), hypertension (5.0%), chronic

renal failure (1.7%), and oliguria (26.7%). This came in line with clinical finding among children with nephrotic syndrome as Edema is the most prominent feature of nephrotic syndrome, and in the beginning, it develops around the eyes and legs. Over time, the edema becomes generalized and leads to increasing weight and the development of ascites or pleural effusions. Hematuria and hypertension may be present less frequently, although these are more prominently seen in nephritic syndrome [19].

Khanna et al showed that the most common clinical findings at presentation were edema (99.5%), fever (50.8%), cough (47.9%) and nausea and vomiting (19.2%) [19].

Regarding lipid profile we found that the NS group had significantly higher levels of TG, cholesterol, and LDL compared to the control group at sampling. Similarly, at the onset of the disease, the NS group had significantly higher levels of triglycerides, cholesterol, LDL, HDL compared to the control group. Within the NS group, there was a significant difference in the TC and LDL between sampling and the onset of the disease, with higher levels observed at the onset.

Chavan et al showed that out of all the 50 subjects screened, 25 (50%) subjects had high total cholesterol, 26 (52%) had high triglyceride, 8 (16%) had abnormal HDL cholesterol and 25 (50%) had high LDL cholesterol. After 4 weeks of steroid therapy though there was significant reduction in lipid components [20].

The findings of this study are similar to those of a study by Sreenivasa et al. and showed a statistically significant difference in lipid parameters except for HDL cholesterol at the onset of disease and at remission in steroid-responsive cases [21].

The finding in the study by Dnyanesh et al., where they measured lipid levels at disease onset and remission in 30 children with nephrotic syndrome, they found significant differences in lipid parameters, except for HDL cholesterol [22].

The present study showed that SRNS showed significantly lower hemoglobin level, higher TC, LDL levels, onset of disease, compared to SDNS.

In line with our findings, **Burlaka** et al showed that serum cholesterol levels were higher in SRSN 11.97 ± 0.38 mmol/L children as compared to 9.89 ± 0.38 µmol/L in children with SRNS. statistically significant differences between SSNS and SRNS regarding WBC count. Blood urea levels were 9.99 ± 0.63 mmol/L and 11.08 ± 0.5 mmol/L [23].

Palaniyandi et al showed that 85 children had onset of disease before 3 years of age and majority had 3+ proteinuria and males predominated in both the groups. The overall consanguinity rates were higher among SRNS group. Triglyceride level >300 mg/dl predominated in SRNS group along with a higher severity of hypoalbuminemia when compared to SSNS group [24]

Conclusion:

From our results we concluded that nephrotic syndrome had generalised hyperlipidemia and abnormal lipid profile occur mostly among cases with SRNS.

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