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Original Article

Role of Persistent Hyperlipidaemia in Relapse of Idiopathic Nephrotic Syndrome

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Abstract

Background & objective: Impact of Nephrotic syndrome due to relapse on children and their families is so diverse and extreme that causes serious physical and mental health problems for a long time. Repeated Hyperlipidemia and frequent long term steroid treatment in relapsed cases add more burdens on already fragile health of these children.

Materials & Methods: This descriptive, observational study was carried out in the Department of Pediatrics, Rajshahi Medical College Hospital over a period of 24 months from July 2015 to June 2017. If a child's age at presentation was between 2 to 8 years of age group of either sex having typical features of nephrotic syndrome(first attack), such as- generalized swelling which started from the face, having abnormal urinary finding (proteinuria 3+ or more and UTP >1gm/m^2/24hrs hypoalbuminemia, hypercholesterolemia but responded to steroid was included in the study. When the child was in remission, serum Lipid profile was done following 10 hours of fasting once again. Then the child was followed up fortnightly for a period of six months from the initial attack for generalized edema and bedside urinary albumin 3+ or more. Results were tested with independent 't' test and χ^2 test to find out the association between high lipid profile during remission with the relapse . A two-tailed P value of 0.05 was considered statistically significant.

Results: All 50 children were divided into two groups on the basis of lipid profile during remission. Group-1 consists of 20 children who had normal lipid profile during remission and group-2 consists of 30 children who had abnormal lipid profile during remission. Both group-1 & 2 had higher mean levels of serum cholesterol, LDL, and TG levels during initial diagnosis. During remission, group-2 patients showed higher mean serum cholesterol (364.60±64.00 mg/dl vs. 189.25±9.02 mg/dl), serum LDL (241.53±58.42 mg/dl vs. 146.65±3.60 mg/dl), and serum TG (225.10±43.79 mg/dl vs. 138.90±8.15 mg/dl). All these differences in lipid profile between these group were statistically highly significant (p=<0.001).Only 2(10%) cases underwent relapse from group-1 out of 20 cases, whereas 16(53.33%) cases underwent relapse out of 30 cases from group-2 within six (6) months follow-up. The difference between group-1 & group-2 was statistically significant (p=0.002).Among the relapsers, mean cholesterol (394.18±43.03 mg/dl vs. 329.50±67.81 mg/dl; p= 0.004) was significantly higher than that of non-relapsers of group-2 patients.

Conclusion: Elevated lipid level, especially serum cholesterol during remission phase may be associated with subsequent relapse in idiopathic childhood nephrotic syndrome.

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Introduction

Nephrotic syndrome (NS) is one of the most common problems among renal diseases in children. It is 15 times more common in children than adults.[1] This clinicopathological condition is characterized by massive proteinuria (>40 mg / m^2/ hour or >1gm/m^2/24 hours in children), hypoalbuminemia (i.e. serum albumin level <2.5 g / dl), oedema and hyperlipidemia.[2,3]

The incidence is 1-3 per 100,000 children of less than 16 yr of age.[4]The age at the onset is usually between 18 months and 6 years.[5]The peak incidence of both minimal change nephrotic syndrome (MCNS) and focal segmental glomerulosclerosis (FSGS) occurs in pre-school age children where 80% of them are less than 6 years old at presentation, with the median age at diagnosis is 2.5 years for MCNS and 6.0 years for FSGS.[6]

Nephrotic Syndrome is categorized into primary or idiopathic and secondary. Primary is not associated with any underlying disease but secondary forms is related to a ream of clinical diseases affecting the kidneys.[7,8] Of them approximately 90% are idiopathic nephrotic syndrome. It includes multiple histologic types: MCNS, mesangial proliferation, FSGS, membranous nephropathy, and membranoproliferative glomerulonephritis.[4,8,9] Among idiopathic nephrotic syndrome, MCNS contribute approximately 85% And most of the children (95%) respond to corticosteroid therapy.[4]

The pathogenesis of MCNS is unclear, but there is a strong evidence of immune dysregulation, chiefly involving cell mediated immunity.[10] Abnormality of T lymphocyte function with secretion of lymphokines, which increases the vascular permeability. Furthermore, the glomerular basement membrane abnormality causes heavy proteinuria.[8] Glomerular basement membrane acts as a selective barrier that prevents excessive loss of protein in the urine in normal condition.[11]

In NS, relapse is defined as massive proteinuria ≥3+ for 3 consecutive days after having gone into remission on previous occasion.[8] Majority of children suffer from relapses. Relapse can be of two types' i.e. infrequent relapses and frequent relapses. Some children may have ≤3 relapses within one year(infrequent relapses) where others may have ≥ 2 relapses within 6 months or ≥4 relapses within one year(frequent relapses).[8,12]

Children with NS have abnormal lipid metabolism which occurs due to increased synthesis and decreased lipid degradation activity.[4]Abnormal lipid metabolism is characterized by increased total cholesterol, triglycerides, and Low Density Lipoprotein (LDL) levels, as well as normal or decreased High Density Lipoprotein(HDL) level.[13] Almost 50% of NS children in the remission phase have dyslipidemia, which is a risk factor for atherosclerosis.[14] Persistence of high lipid level increase the possibility of coronary heart disease and chronic kidney disease.[14,15] So, regular close monitoring of lipid profiles is necessary to anticipate complication, especially in frequently relapsing children.[16,17,18,19] Evaluation and treatment of lipid abnormalities are important aspects in the management of NS in children.[20]

In NS, more than 95% cases of proteinuria is eliminated by oral prednisolone for few weeks. 60 mg/m^2/day in 1 to 3 divided doses for 6 weeks then maintenance by 40 mg/m^2 every other day in the morning for another 6 weeks induce a higher rate of long successful remissions is in the majority of the cases. But 60%–80% of children will have a number of relapses when the drug is tapered off or stopped.[21] Repeated courses of oral prednisolone although effective in relapse, but severe and even fatal side effects may occur at any time if repeated courses of oral corticosteroid given for a longer duration.[8] In a resource limited country like ours, inadequate health care facility, less organized referral system, parent's lack of adequate knowledge about the course of this disease and health seeking behavior of reluctant parents make it difficult for early detection, timely intervention and thus avoiding potentially devastating life threatening consequences of relapse cases.[22] Heath care provider could do more for the children if they could predict which patient had more chance of relapse. Hence this study was carried out to find out abnormal lipid status after

remission and its association with frequency of relapse.

Materials and Methods

This longitudinal type of descriptive study was carried out in the Department of Pediatrics, Rajshahi Medical College Hospital over a period of 24 months from July 2015 to June 2017. Children with 2-8 years of age group of either sex having typical features of nephrotic syndrome (first attack) who fulfilled the selection criteria were enrolled in the study. If a child's age at presentation was between 2 to 8 years with generalized swelling which started from the face, having abnormal urinary finding (proteinuria 3+ or more and UTP >1gm/m^2/24hrs hypoalbuminemia, hypercholesterolemia but responded to steroid was included in the study. NS cases if associated with complication like gross haematuria, hypertension, impaired renal function, hypocomplementemia were excluded. NS cases secondary to other systemic or infective condition such as viral hepatitis, neoplasia, and exposure to drugs or toxic agents known to induce NS were also excluded. Fifty children were selected on the basis of history, thorough clinical examination and relevant investigations (24 hrs UTP, serum albumin, serum lipid profile). To exclude secondary NS some investigations were done (ASO titre, Serum C3, HBsAg, ANA, chest X-ray, serum creatinine).

After initial diagnosis all children were treated according to the protocol (Oral prednisolone 60 mg/m^2/day in divided doses for 6 weeks, followed by 40 mg/m^2/day every alternate day for 6 weeks).When the child was in remission, serum Lipid profile was done following 10 hours of fasting once again. Then the child was followed up fortnightly for a period of six months from the initial attack for generalized edema and bedside urinary albumin 3+ or more. Parents were advised to report immediately whenever they notice generalized edema or bedside urinary albumin 3+ or more during their stay at home. Parents' observation was rechecked by researcher as soon as possible. Results were tested with independent 't' test and χ^2 test to find out the association between high lipid profile during remission with the relapse . A two-tailed P value of 0.05 was considered statistically significant. The protocol of the study was approved by the ethical review committee of Rajshahi Medical College, Rajshahi.

Results

A total of fifty children between 2-8 years age group were included in the study. Serum lipid profile was done during initial phase and after remission.

Table no. I showed mean level of lipids (Serum cholesterol, LDL &TG) at initial phase was higher than normal physiological limit, but HDL value was within normal limit. Whereas mean value of lipids (Serum cholesterol, LDL &TG) after remission though reduced but also remained higher than normal range and HDL value was mildly raised. The difference between initial phase lipid (Serum cholesterol, LDL &TG) and after remission was statistically highly significant (p=<0.001) and the difference between initial HDL and after remission was also statistically significant (p=0.028).

Table I: Comparative study of lipid profile (mean values) during initial phase and after remission

Lipid profile	Initial phase	After remission	't' value	p-value
	Mean±SD	Mean±SD		
Cholesterol (mg/dl)	440.16±80.11	294.10±99.67	12.06	<0.001
HDL(mg/dl)	43.52±3.15	44.34±2.91	–2.27	0.028
LDL(mg/dl)	276.50±36.21	203.58±65.04	7.98	<0.001
TG(mg/dl)	242.40±43.45	190.62±54.59	8.90	<0.001

All fifty children were divided into two groups on the basis of lipid profile during remission. Group 1 consists of twenty children who had normal lipid profile during remission and group 2 consists of thirty children who had abnormal lipid profile during remission.

Table II showed high total cholesterol (364.60±64.00 mg/dl), LDL (241.53±58.42 mg/dl), and TG (225.10±43.79 mg/dl) in group-2 during remission which were all statistically highly significant (p=<0.001). On the other hand HDL (43.63±2.94 mg/dl) was within normal reference value and statistically insignificant ((p=0.58).

Table II: Comparison of lipid profile at remission between group 1 & group 2

Lipid profile	Group 1 Mean±SD	Group 2 Mean±SD	't' value	p-value
Cholesterol (mg/dl)	189.25±9.02	364.60±64.00	-12.08	<0.001
HDL(mg/dl)	45.4±2.58	43.63±2.94	2.18	0.58
LDL(mg/dl)	146.65±3.60	241.53±58.42	-7.22	<0.001
TG(mg/dl)	138.90±8.15	225.10±43.79	-8.67	<0.001

Independent Samples 't' Test

Table III showed only 2(10%) cases underwent relapse from group 1 out of 20 cases, whereas 16(53.33%) cases underwent relapse out of 30 cases from group 2 .The difference between group 1 & group 2 was statistically significant (p=0.002).

Table III: Number of relapse cases within six months follow-up period

Group	Number of cases with relapse	Number of cases without relapse	p-value
Group 1 (n=20)	2(10%)	18(90%)	
Group 2 (n=30)	16(53.33%)	14(46.66%)	0.002
Total	18(36%)	32(64%)	

χ^2= 9.780 df=1 p=0.002

Table IV showed mean serum cholesterol level in relapse group (2 cases from group-1 and 16 cases from group-2) during remission was higher than that of non-relapse group (18 cases from group-1 and 14 cases from group-2). It showed the difference was statistically highly significant (p=<0.001). Mean TG level in relapse group during remission was also higher than that of non-relapse group and the difference was statistically highly significant

(p=<0.001). Mean HDL level of both relapse and non-relapse group during remission was within normal physiological range. Mean serum LDL level in relapse group was higher than that of non-relapse group and the difference was statistically significant (p=<0.003).

Table IV: Mean level of lipid in relapse and non-relapse group during remission

	S. Cholesterol (mg/dl)	S. HDL (mg/dl)	S. LDL (mg/dl)	S.TG (mg/dl)
Relapse (n=18)	371.77±76.73	43.83±3.05	239.16±57.50	227.72±52.93
Non relapse (n=32)	250.40±83.66	44.62±2.83	183.56±61.02	169.75±45.88
P-value	<0.001	0.361	0.003	<0.001

Independent Samples‘t’ Test

Table V showed mean levels of lipids between relapse cases and non-relapse cases of group 2 (high lipids during remission). Mean serum cholesterol, LDL, TG level was higher in relapse group than non-relapse group. Whereas, HDL remained almost unchanged. But, mean serum cholesterol between relapse cases was significantly higher than non-relapse cases and that was statistically significant (p=0.004). Other lipids did not differ significantly between two groups.

Table V: Mean levels of lipids between relapse and non-relapse cases of group 2 children.

Lipid profile	Non-Relapse Mean±SD	Relapse Mean±SD	‘t’ value	p-value
Cholesterol (mg/dl)	329.50±67.81	394.18±43.03	3.16	0.004
HDL(mg/dl)	43.85±3.18	43.43±2.80	-0.38	0.704
LDL(mg/dl)	231.21±67.18	250.56±50.01	0.90	0.375
TG(mg/dl)	209.92±37.51	238.37±45.66	1.84	0.075

Independent Samples ‘t’ Test

Table VI showed mean levels of lipids among relapse cases and non-relapse cases of group-2 (Abnormal lipids during remission) patients during remission. Mean serum cholesterol, LDL, TG level was higher in relapse group than non-relapse group. Whereas HDL remain almost unchanged. But mean serum cholesterol among relapse cases was significantly higher than non-relapse cases and that was statistically significant (p=0.004). Other lipids did not differ significantly in between two groups.

Table VI: Mean levels of lipids among relapse and non-relapse cases of group 2 patients after remission

Lipid profile	Non-Relapse Mean±SD	Relapse Mean±SD	‘t’ value	p-value
Cholesterol (mg/dl)	329.50±67.81	394.18±43.03	3.16	0.004
HDL(mg/dl)	43.85±3.18	43.43±2.80	-0.38	0.704
LDL(mg/dl)	231.21±67.18	250.56±50.01	0.90	0.375
TG(mg/dl)	209.92±37.51	238.37±45.66	1.84	0.075

Independent Samples ‘t’ Test

Discussion

Merouani A et al had observed that despite the disappearance of proteinuria, hyperlipidemic profiles were present in nearly half of their nephrotic children at remission. They also observed that hyperlipidemic profiles correlated significantly with the number of relapse episode.[16] Mahmud S et al also observed similar findings and they also found correlation between serum cholesterol and relapse.[23] The results of above mentioned study were consistent with the present study.

Kawasaki Y et al had shown that lipid abnormality was significantly related with number of relapse but they also observed that mean age of presentation did not influence the relapse.[24] The present finding is partially consistent with above mentioned study and relation of mean age at presentation with frequency is beyond the scope of this study.

In the present study the initial lipid profiles at the time of diagnosis of nephrotic syndrome significantly higher in both group 1 (cholesterol = 398.95±59.79, LDL = 275.40±24.01, TG = 212.25±31.72) and group-2 (cholesterol = 467.63±80.92, LDL = 277.23±42.85, TG = 262.50±38.54) except HDL values. Sreenivasa B et al in their study shown that mean value of serum cholesterol, TG, LDL and VLDL were significantly higher except HDL.[25] These findings are similar with this study. Sreenivasa B et al also observed that serum lipids decreased significantly during remission which is opposite to the present study.[25]

In the present study, 30(60%) children had abnormal lipid profile and 20(40%) children had normal lipid profile during remission. They were divided into two groups on the basis of lipid profile during remission 16 children developed relapse out of 30 children in group 2 whereas 2 children developed relapse out of 20 children and the difference was statistically significant (0.002). Similar findings observed by Lawang SA et al and Mahmood S et al.[19,23]

The present study had showed higher value of serum lipid level during remission may be associated with future relapse.

Conclusion

Elevated lipid level, especially serum cholesterol during remission phase may be associated with subsequent relapse in idiopathic childhood nephrotic syndrome.

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