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Plasma Lipid Profile - Prognostic Factor in Nephrotic Syndrome – A Prospective Study.

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ABSTRACT

Background: Nephrotic Syndrome is one of the most common glomerular disorders of childhood. Relapse rate after steroid discontinuation is 39-59%. Hyperlipidemia is one of the cardinal features in patients with Nephrotic Syndrome. Cases with increased serum levels of cholesterol and LDL have also been reported even after months or years in remission. The persistent hyperlipidemia correlates well with the duration and frequency of the relapses, even during the remission. **Aim:** To study the correlation between remission phase hyperlipidemia and subsequent relapse in Nephrotic Syndrome. **Methods:** Sixty five children were included in this cohort study at Kanyakumari Medical College & Hospital, Asaripallam. Fasting lipid profile is estimated at the acute phase of Nephrotic Syndrome before starting steroid therapy and 10 weeks after remission. They were followed up for six months from the time of remission to determine the occurrence of relapse. **Results:** Among the 60 included patients, 22 cases had their first episodes and 38 were infrequent relapse. Persistent hypercholesterolemia was observed in ten cases, out of which, seven cases developed relapse. Also, persistent hypertriglyceridemia was seen in 34 cases, out of which, 19 cases developed relapse. However, in the remission phase, hypercholesterolemia (chi sq= 5.090, p=0.024) and hypertriglyceridemia (chi sq= 10.22, p=0.001) were significantly associated with relapse. **Conclusion:** The role of dietary management and anti-triglyceridemic drugs to prevent progressive renal injury and subsequent relapse in this subgroup of patients' needs to be evaluated.

Keywords: Nephrotic syndrome, Lipid profile, Hypercholesterolemia.

INTRODUCTION

In Children most common Nephrotic Syndrome is Idiopathic Nephrotic Syndrome, also called "Nephrosis". It is characterized by proteinuria, hypoalbuminemia, edema and hyperlipidemia. Hyperlipidemia, one of the cardinal features in patients with Nephrotic Syndrome. Hyperlipidemia might affect the kidneys directly or indirectly. In Nephrotic Syndrome, hyperlipidemia occurs partially as the result of a generalized increase in hepatic protein synthesis, inclusive of the overproduction of lipoproteins. In addition, fewer lipids are transported into the adipose tissue due to the reduced activity of lipoprotein lipase in active Nephrotic Syndrome.

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Serum albumin normalizes soon after the proteinuria clears; but hypercholesterolemia takes 6 to 10 weeks or more to resolve.[1] Cases with increased serum levels of cholesterol and LDL have also been reported even after months or years in remission.[2]

The persistent hyperlipidemia correlates well with the duration and frequency of the relapses, even during the remission. Further, the intensity of hyperlipidemia is also related to the severity of proteinuria and hypoalbuminemia.[3]

The projected annual incidence of NS is 2–7/100,000 children, affecting mostly those under 6 years of age. Children continue to experience disease flare-ups for a considerable period of time from onset. Srinivasa et al studied about relationship of lipid profile during and remission. Very fewer studies are available about remission phase hyperlipidemia in India. Hence the study were conducted to select high risk patients with close monitoring of remission phase lipid levels.[4]

Aim

To study the correlation between remission phase hyperlipidemia and subsequent relapse in Nephrotic Syndrome.

MATERIALS AND METHODS

The present study was a prospective cohort study conducted over one year duration. The study participants included the children who were admitted

for the management of Nephrotic Syndrome at pediatric ward of Government Kanyakumari medical college & Hospital, Kanyakumari Medical College, Asaripallam. Children (aged 1 to 12 years) who presented with the first episode / subsequent relapses of Nephrotic Syndrome were included in the study. However, children with secondary Nephrotic Syndrome, Steroid resistant Nephrotic Syndrome, and Steroid dependent Nephrotic Syndrome associated with frequent relapses and Nephrotic Syndrome associated with other systemic illness / complications were excluded from the study.

Detailed clinical history was elicited and a thorough clinical examination was performed. The following investigations were performed - 24 hr urinary protein, spot PCR, serum albumin, lipid profile, urine albumin, USG abdomen, Chest X- Ray, TB screening, baseline blood investigations and urine culture and sensitivity.

RESULTS

A total of 65 cases were enrolled of whom five were excluded. Among the cases excluded, two children had steroid resistant Nephrotic Syndrome, two children presented with steroid dependent Nephrotic Syndrome while one child was lost to follow up. Among the 60 included patients, 22 cases had their first episodes and 38 were infrequent relapsers. Fifty patients (83%) attained remission in <2 weeks while ten patients (17%) took 2 to 6 weeks to attain remission.

Seventy percentages of the children presenting with Nephrotic Syndrome belonged to 1 to 6 years of age group with males being predominantly affected. The precipitating factors included ARI and UTI in 33% and 23% of the cases, respectively while it was unknown in 44% of the cases. Among the culture positive UTI cases, Klebsiella was the most common organism isolated (6 cases), while E.coli and Proteus were also isolated in 4 and 2 cases, respectively.

Among the presenting symptoms edema was the most common (100% incidence) followed by oliguria 81.7%.Urinary proteinuria was evaluated using the sulphosalicylic acid test. It was observed that 12 cases (20%) presented with moderate proteinuria (+++) and 48 cases (80%) presented with severe proteinuria (++++). Mean 24 hours urinary protein levels ranged from 0.75 to 3.89 g/dl with a mean of 1.89 g/dl. Likewise, serum albumin ranged between 1.2 - 2.8 g/dl with a mean of 1.855g/dl. In the present study, the infrequent relapses had lower mean serum albumin levels (1.45 g/dl) when compared to the first episode cases (2.07 g/dl). Looking into the distribution of hypoalbuminemia, mild, moderate and severe hypoalbuminemia were seen in 23.3%, 45 % and 31.7 % cases, respectively. In the present study, most of the children had moderate hypoalbuminemia in the acute phase. In the present study, 83 % of the children attained remission within 2 weeks of initiation of therapy, while 17% of the children attained remission in 2 - 6 weeks. After a follow up of the patients unto 6 months, relapse was observed in 23 (38.3%) cases. Among the 23 cases which relapsed, 9 cases were those with the first episode of Nephrotic Syndrome.

Table 1:- Comparison of baseline characteristics between the relapsers and non relapsers.

Characteristic	Non-relapser	Relapser	P value
Age	4.77±2.67	5.61±2.48	0.229
Duration	5.97±4.22	13.66±29.22	0.120
Serum Urea	24.41±7.24	24.7±8.76	0.890
Serum Creatinine	0.703±0.1301	0.709±0.1345	0.865
Serum Albumin	1.914±0.38	1.761±0.405	0.144
24 hours urinary protein	1746.7±697.06	2017.09±963.18	0.219
Spot PCR	14.86±8.74	20.97±10.44	0.018**

**p<0.05 was considered to be statistically significant

[Table 1] Shows the comparison of baseline characteristics between the relapsers and non relapsers which were comparable. Spot PCR was significantly different between relapsers and non relapsers.

Table 2: Lipid profile during acute and remission phases for all subjects.

Lipids	Mean	SD	Min mg/dl	Max mg/dl	P value
CHO – acute	360.88	100. 17	205	566	<0.01**
CHO – remission	167.68	28.1	102	274	
TG-acute	296.12	112.9	115	571	<0.01**
TG- remission	160.32	48	85	413	
LDL-acute	265.72	97	110	460	<0.01**
LDL-remission	94.73	30	27	203	
VLDL-acute	59.25	22.8	19	114	<0.01**
VLDL-remission	32.5	10.469	17	83	

HDL-acute	38.1	4.82	25	58	<0.01**
HDL-remission	41	3.125	32	48	
LDL:HDL ratio- acute	7.136	2.85	2.8	16	<0.001*
LDL:HDL ratio-remission	2.351	0.78	0.6	5.4	

**p<0.05 was considered to be statistically significant

[Table 2] shows the lipid profile during the acute and remission phases for all subjects. A statistically significant difference was found in the mean values of lipid profile parameters measured between during acute and remission phases. (p value < 0.01).

Table 3: Lipid profile during acute and remission phases for relapsers.

Lipids	Mean	S.D	Minimum (mg/dl)	Maximum (mg/dl)	P value
CHO – acute	396.65	106	205	566	< 0.01**
CHO – remission	171.22	33.5	125	274	
TG-acute	316.26	141.6	128	571	< 0.01**
TG- remission	179.7	35.7	107	256	
LDL-acute	269.2	100.9	126	460	< 0.01**
LDL-remission	93.96	35	29	203	
VLDL-acute	63.22	28.28	26	114	< 0.01**
VLDL-remission	37.17	8.75	21	61	
HDL-acute	37.22	5.248	25	52	< 0.02**
HDL-remission	40.13	2.222	37	48	

**p<0.05 was considered to be statistically significant

On observing the lipid profile during acute and remission phase in the 23 relapsed cases, a statistically significant difference was found in the mean values of lipid profile parameters measured between during acute and remission phases. (p value < 0.01). [Table 3].

Table 4:- Acute phase lipid abnormalities in relapsers Vs non-relapsers.

Lipids	Non relapsers	Relapsers	P value
Hypercholesterolemia	37(100)	23(100)	-
Hypertriglyceridemia	36(97.3)	22(95.7)	0.730
High LDL	35(94.6)	22(95.7)	0.922
High LDL:HDL	26(70.3)	19(82.6)	0.283

**p<0.05 was considered to be statistically significant

Table 5: Remission phase lipid profile abnormalities in relapsers Vs non-relapsers.

Lipids	Non Relapsers	Relapsers	P value
Hypercholesterolemia	3(8.1)	7(30.4)	0.024**
Hypertriglyceridemia	15(40.5)	19(82.6)	0.001**
High LDL	3(8.1)	1(4.3)	0.570
High LDL:HDL	0	1(4.3)	0.201

**p<0.05 was considered to be statistically significant

Table 6: Predictors of relapse in children with nephritic syndrome using Logistic regression.

Predictors	Adjusted OR	SE	Z	Significance	95% CI of OR
Spot PCR	1.09	0.39	2.45	0.014**	1.02,1.17
Remission phase hypercholesterolemia	4.82	4.25	1.78	0.075	0.86,27.13
Remission phase hypertriglyceridemia	7.26	5.22	2.76	0.006**	1.77,29.72

**p<0.05 was considered to be statistically significant

The abnormalities in lipid profile parameters were compared between the relapsers and non relapsers in both the acute and remission phases. [Table 4 & Table 5]. In the acute phase, there were no significant differences between the lipid abnormalities manifested by the relapsers and non relapsers. However, in the remission phase, hypercholesterolemia (chi sq= 5.090, p=0.024) and hypertriglyceridemia (chi sq= 10.22, p=0.001) were significantly associated with relapse. Further, on performing logistic regression analysis, remission phase hypertriglyceridemia (adjusted OR= 2.76, p=0.006) and spot PCR (adjusted OR= 2.45, p=0.014) were found to be significant predictors of relapse [Table 6].

DISCUSSION

All children with primary Nephrotic Syndrome develop hyperlipidemia but change is marked in patients with minimal change. Patient with

Nephrotic syndrome have increased serum cholesterol, VLDL, LDL, TG.HDL is not increased in these patients because it is lost in the urine. Shafrir et al. observed that when the level of albumin decreases, free fatty acids and other amphipathic compounds bind to VLDL instead of albumin. So, the interaction between TG and lipoprotein lipases is altered. The unbound free fatty acids decrease the rate of VLDL clearance by inhibiting lipoprotein lipases enzyme.[5] Warwick GL et al. (1990) proposed that the factors that precipitated the hyperlipidemia included decrease in circulating albumin or plasma oncotic pressure which in turn might be responsible for the stimulation of a general increase in hepatic protein and lipoprotein synthesis. Persistent hypercholesterolemia and hypertriglyceridemia are common in patients who have treatment – resistant Nephrotic syndrome.[6]

In the present study, fasting sample of blood was taken for lipid profile evaluation at the time of admission and then, 10 weeks after remission. These children were followed up for six months to look for further relapse. Most of the children in our study belonged to the age group of 1-6 years (70%), while 30% of the children belonged to 6 to 12 years of age group.

The age incidence of the present study was comparable or slightly higher when compared to the other reports in existing literature.[7-11] The total number of children included in the present study was 60 - 36 males and 24 females. Among these children, it was observed that 38 children (28 males + 10 females) were found to have infrequent relapse, while 22 children (8 males + 14 females) presented with their first episode. The gender wise ratio in terms of incidence of first episodes or infrequent relapses were comparable with the studies of Nanjundasamy et al and Beth Avgot et al.[12-14]

The initial episode of idiopathic Nephrotic Syndrome, as well as subsequent relapses, usually followed minor infections and uncommonly, reactions to insect bites, bee stings, or poison ivy.[15] In the present study, ARI was the most common known precipitating factor and this finding was concurrent with Kasim Rahi et al.[16]

Children with Nephrotic Syndrome most commonly presented with periorbital oedema/ generalized swelling, decreased urine output and pallor. All the sixty children presented with edema either periorbital or generalized, followed by oliguria present in 81.7% children. Pallor was seen in 38% children. Most of the studies showed that edema was the cardinal clinical feature of Nephrotic Syndrome. The proportion of patients with pallor in the present study was comparatively higher than other studies and this could be attributed to the nutrition or severity of the disease.

In the present study, severe proteinuria was seen in 80% children and moderate proteinuria in 20 % of the children. Shah et al reported 74 % and 26 % of the cases with severe and moderate proteinuria, respectively.[17] In Children with infrequent relapse, mean serum albumin value was 1.45 g/dl. This was lower than in children with their first episodes (2.072g/dl) It was thus observed that infrequent relapsers had more severe hypoalbuminemia than the first episode cases.

In the present study, 19 cases (31.7%) had severe hypoalbuminemia, 27 cases (45%) had moderate hypoalbuminemia and 14 cases (23.3%) had mild hypoalbuminemia. Correlation between serum Albumin and serum cholesterol at the acute phase of the disease was performed and it revealed a statistically significant inverse relation ($p<0.01$) between them in the present study. Appel GB et al. (1985) also observed a significant correlation between the total plasma cholesterol concentration and both the plasma albumin concentration and plasma oncotic pressure.[18]

The authors observed a statistically significant difference was in the mean blood cholesterol levels during the acute and remission phases which was also concurrent with the study of Sitti Aizah Lawang et al. The significant difference that was observed in the mean serum triglyceride levels during the acute and remission phases were comparable again with the reports of Sitti Aizah Lawang et al.[19]

Further, there was a statistically significant reduction ($p <0.01$) in LDL and HDL values during the remission phase in comparison to acute phase LDL values. The results were similar with that of SittiAizah Lawang et al.[19] There was also a significant difference in the mean values of VLDL in the acute and remission phases.

In our study, Persistent hypercholesterolemia was observed in ten cases, out of which, seven cases developed relapse. Also, persistent hypertriglyceridemia was seen in 34 cases, out of which cases developed relapse.[20]

In the acute phase, there were no significant differences between the lipid abnormalities manifested by the relapsers and non relapsers. However, in the remission phase, hypercholesterolemia (chi sq= 5.090, p=0.024) and hypertriglyceridemia (chi sq= 10.22, p=0.001) were significantly associated with relapse. Mahmud et al found that among the relapsers, mean blood cholesterol level was significantly higher than that of non relapsers ($P <0.05$). They concluded that serum cholesterol level could be considered as a predictor of relapse in childhood idiopathic nephrotic syndrome.[22] The triglyceride levels of the present study were comparable with the reports Sitti Aizah Lawang et al. ($p <0.035$).[19] Further, on performing logistic regression analysis, remission phase hypertriglyceridemia (adjusted OR= 2.76, p=0.006) and spot PCR (adjusted OR= 2.45, p=0.014) were found to be significant predictors of relapse. Among relapser, all of them had single relapse during six

months of follow up. They seem to follow infrequent relapse course.

CONCLUSION

Persistent triglyceridemia is a marker for relapse. The role of dietary management and anti-triglyceridemic drugs to prevent progressive renal injury and subsequent relapse in this subgroup of patients needs to be evaluated. Further, the exact duration of persistent hypertriglyceridemia has to be evaluated by further studies. Also, more studies are required to study the efficacy of lipid lowering agents in children to confirm safety and efficacy.

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