ORIGINAL ARTICLE

Carotid intima media thickness in children with nephrotic syndrome: an observational case control study

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ABSTRACT

Carotid intima media thickness (cIMT) is considered as a surrogate marker for the various cardiovascular events that complicate nephrotic syndrome (NS). The present work was conducted to study cIMT in children with NS and to find out its correlation with dyslipidemia and other risk factors. This was a case control study conducted at a tertiary care hospital in children with NS who were more than 2 years with normal serum complement, being on therapy for NS for at least 1 year, glomerular filtration rate more than 90 ml/minute/1.73 m^2 and absence of acute infection in previous 3 months. Sixty six children with NS constituted the case material and 128 age and sex matched children were taken as control. The mean age in case and control cohort was 6.71 ± 3.3 and 7.89 ± 3.95 years, respectively. The mean age of onset of illness was 4.32 ± 2.25 years. The mean duration of illness was 2.39 ± 1.44 years. Thickness of cIMT was higher in NS children as compared to control group in all the ages, but this difference was statistically significant only after 4 years of age. There was statistically significant, but weak positive correlation between cIMT and age of NS children, duration of disease and number of relapses. There was no correlation of cIMT with hypertension, body mass index, serum creatinine, and dyslipidemia. A negative, but statistically insignificant correlation of cIMT was found with serum albumin and serum cholesterol.

KEYWORDS

Carotid intimal-medial thickness; Nephrotic syndrome; Children; Dyslipidemia; Hypertension; Body mass index.

INTRODUCTION

Nephrotic syndrome (NS) is complicated by infection, thromboembolic events, cardiovascular disease, acute renal failure and bone mineral loss [1]. In children with NS, thromboembolic complications vary between 2% and 5% which is

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less than in adults [2–8]. Few studies have reported persisting lipid abnormalities during remission [8] and severe persistent proteinuria as a risk factors for later development of atherosclerosis [9].

Currently, increased carotid intima media thickness (cIMT) has been accepted as a reliable marker for atherosclerosis and its complications, such as cardiovascular disease, including coronary artery disease and myocardial infarction, and stroke [10]. Increased cIMT in children is also associated with other cardiovascular risk factors, such as familial hypercholesterolemia, growth hormone deficiency, diabetes and other arteriopathic diseases, such as Williams syndrome and Kawasaki disease [11]. There are nearly fivefolds increase chances of stroke or heart attack rates with increased cIMT [12].

This work has been planned to study the cIMT in NS children and its correlation with dyslipidaemia and other risk factors that influence cIMT in paediatric age group.

MATERIALS AND METHODS

This is an observational case control study carried out in Department of Paediatrics, Baba Raghav Das (BRD) Medical College, Gorakhpur from January 2016 to June 2016. The study protocol was approved by the Institution Ethics Committee. Well-informed written consent in local language, after explaining the purpose and the method of study, was taken from mothers/ guardians of each patient. G power version 3.1.9.2 was used for sample size measurement using the study by Hooman et al. [13].

Inclusion and exclusion criteria

Nephrotic syndrome (NS) children, with age more than 2 years at the time of study with normal serum complement, being on therapy for NS (continuous or interrupted) for at least 1 year, glomerular filtration rate (GFR) more than 90 ml/minute/1.73 m² and absence of acute infection in previous 3 months, constituted case material. NS children with essential hypertension, diabetes mellitus, obesity, and patients with history of familial hypercholesterolemia were excluded from the study. One hundred twenty eight, age, and sex matched children who visited the hospital for other reasons constituted the control group.

Study procedure

A detailed history was taken from each patient, including past medical and drug history. A detailed examination was done in all the patients, including measurement of weight and height, calculation of body mass index, measurement of arterial blood pressure, examination for oedema and cardiac examination to ensure none of our patients had congenital or rheumatic heart disease. Normotension, prehypertension and hypertension was defined as systolic or diastolic blood pressure <90th percentile, between 90th and 95th percentile (>120/80 even if below the 90th percentile) and >95th percentile for age, height and sex, respectively. All patients underwent laboratory investigations and ultrasonography was done for the assessment of cIMT. The findings were recorded on a predefined working proforma.

Diagnostic work up

Laboratory investigation included levels of blood urea, creatinine and albumin, and urine examination. Plasma creatinine was measured by Jaffe method using creatinine kit (Pars Azmun) Biolis 24 I Premium device (Tokyo boeki medical system). All children underwent a complete lipid profile including total cholesterol, high-density lipoprotein (HDL), low-density lipoproteins (LDL), very-low-density lipoprotein (VLDL) and triglycerides. Cholesterol and triglyceride were measured by enzymatic end point method. HDL was removed after precipitation of LDL using phosphotungstic acid/magnesium by enzymatic end point method. LDL cholesterol was calculated by Friedwald's formula [14]. GFR was calculated by Schwartz formula [15].

GFR = K × Height (cm)/Pcr

Pcr: Plasma creatinine

K: Constant, its value is 0.55 in 1 and 12 years, 0.57 in females >of 12 years and 0.70 in males >12 years.

GFR more than 90 ml/minute/1.73 m² was considered as normal.

cIMT measurement

Measurement of cIMT was done according to Manheims Consensus Guideline 2011 [16], by

an experienced radiologist who was blind folded to patient's status. The ultrasound measurement was obtained using a single ultrasound machine TOSHIBA Nemio with a linear high frequency transducer (7.5 MHz).The patients were made to lie in supine position and head turned slightly to the contra lateral side with a slightly overextended neck. After 10 minutes of rest, the arterial wall segment was assessed in a longitudinal view, strictly perpendicular to the ultrasound beam, with both walls clearly visualized in order to achieve diameter measurements. It will be formed by two parallel lines, which consist of the leading edges of two anatomical boundaries: the lumen-intima and media-adventitia interfaces. Measurements were obtained from the far wall of both common carotid arteries 10–20 mm proximal to bifurcation. The measurements were carried on frozen images demonstrating the thickest intima-media thickness (IMT) complex with callipers placed on a zoomed CCA image. The measurements were made on each side; the mean of left and right common carotid artery was used in the study.

Statistical analysis

Data was presented as percentages, means, and standard deviations. Chi square test was used to study frequency distribution between groups. In case the frequency was less than 5, Fisher's exact test was used. Univariate analysis for group comparisons of means was performed using Unpaired Student-*t* test. Correlation between the continuous variables and cIMT was studied using Pearson's correlation coefficient. *p* value was considered as significant at <0.05. Confidence interval was taken at 95%.

RESULTS

A total of 124 NS children were screened from admitted and outdoor patients at Paediatric Department of Baba Raghav Das (BRD) Medical College, Gorakhpur. Sixty six children with NS constituted the case material and 128 age and sex matched were taken as control (Table 1). The mean age in case cohort was 6.71 ± 3.4 years and in control cohort was 7.89 ± 3.95 years. Maximum numbers of children were in the age group 4–10 years in both cohorts. Male:female ratio were 1.54 and 1.46, respectively.

Of the 66 NS children, 41 (62.12 %) were in relapse and 25 (37.87%) were in remission at the time of admission. The mean age of onset of illness was 4.32 ± 2.25 years. Steroid responsive, steroid dependent and steroid resistant cases were 58 (87.87%), 5 (7.57%) and 3 (4.54%), respectively.

The mean duration of illness was 2.39 ± 1.44 years. Number of relapses of the disease was at an

Table 1. Baseline characteristics of children with nephrotic syndrome and control group.

Characteristics		Cases *n* = 66 (%)	Control *n* = 128 (%)	*p* value
Age (years)	2–4	13 (19.69)	18 (14.06)	x^2 = 4.497
	4–10	38 (57.57)	62 (48.43)	*p* > 0.05
	>10	15 (22.72)	48 (37.5)	
Sex	Male	40 (60.6)	76 (59.37)	x^2 = 0.028
	Female	26 (39.39)	52 (40.63)	
	+2 to+1	4 (6.06)	6 (4.69)	*p* > 0.05
BMI (SD)	+1 to −1	43 (65.15)	78 (60.94)	x^2 = 0.810
	−1 to −2	17 (25.76)	38 (29.69)	*p* > 0.05
	-2 to -3	2 (3.03)	6 (4.69)	
Blood Pressure (mm of Hg)	Normotensive	44 (66.67)	92 (71.87)	x^2 = 0.581
	Prehypertensive	12 (18.18)	19 (14.8)	
	Hypertensive	10 (15.15)	17 (13.28)	*p* > 0.05

BMI, body mass index; SD, standard deviation.

average of 3.46 ± 1.34. More than four relapses during the entire period of study were seen in 16 (24.24 %) cases only. Baseline characteristics were comparable in both the groups (Table 1). Table 2 shows total cholesterol, LDL, HDL, triglyceride and VLDL levels in NS children.

Thickness of cIMT in children with NS and control group is displayed in Table 3. cIMT increased with advancing age in both the groups. Thickness of cIMT was higher in NS children as compared to control group in all the ages, but this difference was statistically significant ($p < 0.0001$) only after 4 years of age.

Correlation of the thickness of cIMT with various characteristics of NS is shown in Table 4. We found a statistically significant but weak positive correlation between cIMT and age of children with ($r = 0.428$, $p < 0.001$), duration of disease ($r = 0.435$, $p < 0.001$) and number of relapses ($r = 0.435$, $p < 0.001$). There was no correlation of cIMT with hypertension ($r = 0.115$, $p > 0.05$), BMI ($r = 0.173$, $p > 0.05$) or serum creatinine ($r = 0.139$, $p > 0.05$). When cIMT was compared with serum lipid levels, we found no correlation of cIMT with LDL ($r = 0.043$, $p > 0.05$), HDL ($r = 0.091$, $p > 0.05$), triglyceride ($r = 0.116$, $p > 0.05$) or VLDL ($r = 0.034$, $p > 0.05$). A negative, but statistically insignificant correlation of cIMT was found with serum albumin ($r = -0.120$, $p > 0.05$) and serum cholesterol ($r = -0.089$, $p > 0.05$).

Table 2. Dyslipidemia in children with nephrotic syndrome.

Lipid profile	Mean ± SD (mg/dl)
Total cholesterol	349.00 ± 131.7
LDL	180.37 ± 80.59
HDL	48.58 ± 4.09
Triglyceride	182.27 ± 66.46
VLDL	54.07 ± 22.03

HDL, high-density lipoprotein; LDL, low-density lipoproteins; VLDL, very-low-density lipoprotein.

DISCUSSION

This work was carried out in a tertiary care hospital to study the cIMT in NS children and its correlation with dyslipidaemia and other risk factors. In our study, thickness of cIMT was higher in NS children as compared to other children. A statistically significant positive correlation was found between cIMT and age of children with NS, duration of disease, and number of relapses. A negative, but statistically insignificant correlation of cIMT was found with serum albumin and serum cholesterol level.

In the present study, the mean age of onset of NS was 4.32 ±2.25 years. A similar result was observed by Safaei and Maleknejad [17] but other researchers [18] had reported the mean age of onset at 7.9 ± 5.1 years. The lower age of onset in our study could be because the maximum cases of NS would be of minimal change type, which has lower age of onset as compared to other types.

In our study, the mean duration of disease was 2.39 ±1.44 years. A statistically significant but weak positive correlation was found with cIMT. Other researchers [13,19,20,21] had also reported similar results.

The number of relapses in our study was 3.46 ± 1.34, which showed a statistically significant positive correlation with cIMT. Other studies have also reported similar results [19,20]. However, to

Table 3. Carotid intima media thickness (cIMT) in children with nephrotic syndrome and control group.

Characteristic		cIMT (Case) mean ± SD(n)	cIMT (Control) mean ± SD(n)	*p* value
Age (years)	2-4	0.32 ± 0.09 (13)	0.29 ± 0.06(18)	>0.05
	4-10	0.38 ± 0.09 (38)	0.32 ± 0.06(62)	0.0001
	≥10	0.45 ± 0.09 (15)	0.33 ± 0.06(48)	0.0001

cIMT, carotid intima media thickness; SD, standard deviation.

Table 4. Correlation of characteristics of nephrotic syndrome children with cIMT.

Characteristics		cIMTmean ± SD(n)	*p* value
Age(years)	2–4	0.32 ± 0.09 (13)	
	4–10	0.38 ± 0.09 (38)	*r* = 0.428
	≥10	0.45 ± 0.0 (15)	*p* < 0.001
Blood Pressure (mm of Hg)	Normotensive	0.38 ± 0.19 (44)	
	Prehypertensive	0.37 ± 0.29(12)	*r* = 0.115
	Hypertensive	0.41 ± 0.39(10)	*p* > 0.05
	+2 to+1	4 (6.06)	
BMI(SD)	+1 to −1	43 (65.15)	*r* = 0.173
	−1 to −2	17(25.76)	*p* > 0.05
	-2 to -3	2(3.03)	
Duration of Disease (years)	1-2	0.35 ± 0.09 (27)	*r* = 0.435
	2-4	0.39 ± 0.09 (24)	*p* < 0.001
	≥4	0.47 ± 0.09 (15)	
Number of relapses	<4	0.36 ± 0.09 (45)	*r* = 0.435
	≥4	0.44 ± 0.007 (21)	*p* < 0.001
Serum albumin (mg/dl)	35-40	0.39 ± 0.09(56)	*r* = -0.120
	40-55	0.37 ± 0.1(10)	*p* > 0.05
Serum creatinine (mg/dl)	≤0.7	0.38 ± 0.09 (49)	*r* = 0.139
(mg/dl)	>0.7	0.4 ± 0.09 (17)	*p* > 0.05
Lipids (mg/dl)			
Serum	≥400	0.39 ± 0.09 (24)	
cholesterol	200-400	0.37 ± 0.09(30)	*r* = −0.089
	≤200	0.42 ± 0.09 (12)	*p* > 0.05
Serum LDL	≥400	0.30 ± 0.09(2)	
	200-400	0.36 ± 0.09(15)	*r* = 0.043
	<200	0.4 ± 0.09 (48)	*p* > 0.05
Serum HDL	30-45	0.38 ± 0.09 (33)	*r* = 0.091
	45-60	0.38 ± 0.09 (33)	*p* >0.05
Serum triglyceride	>300	0.30 ± 0.09 (3)	
	100-300	0.39 ± 0.09 (55)	r=0.116
	<100	0.32 ± 0.08 (7)	p>0.05
Serum VLDL	>80	0.34 ± 0.09 (5)	
	50-80	0.41 ± 0.09 (32)	r=0.034
	20-50	0.37 ± 0.09(29)	p>0.05

cIMT, carotid intima media thickness; HDL, high-density lipoprotein; LDL, low-density lipoproteins; SD, standard deviation; VLDL, very-low-density lipoprotein.

establish it as an independent risk factor, further studies are needed as with the number of relapses, steroid use also increases and that may confound the results.

There was no correlation between cIMT and BMI in our study, but Litwin et al. [22] reported a weak positive correlation between them. However, on subgroup analysis they reported hypertensive

obese had statistically significant correlation. In our study none of the patients was obese, which may be the reason for this finding.

We had not found any correlation of cIMT with blood pressure, and this could be because of the fact that only 15.15% of our NS children were hypertensive. Other researchers [13] had shown a weak positive correlation of cIMT with blood pressure. We found no correlation of cIMT with serum creatinine level.

In our study, serum albumin had negative, but insignificant correlation with cIMT. It has also been discussed elsewhere [23] how hypoalbuminaemia contributes to reduce lipoprotein catabolism in NS children and hence leading to dyslipidaemia. Hypoalbuminaemia also results in endothelial cells oedema which also contributes to increase in cIMT. Similar results were also reported by other researchers [13,24].

We found no correlation of cIMT with LDL, HDL, triglyceride, and VLDL but a statistically insignificant negative correlation with cholesterol level was found. Other researchers [13,25,26] have also not shown any correlation of cIMT with dyslipidaemia.

CONCLUSIONS AND LIMITATIONS OF THE STUDY

cIMT was more in children with NS as compared to other children. Thickness of cIMT increases with duration of disease, number of relapses, and advancing age. As increased cIMT is a surrogate marker of atherosclerosis in children, assessment of cIMT can be of benefit on the long term care of NS children. The main limitation of this study is lack of long term follow up to see the changes in cIMT over a period of time, particularly during remission phase. Other limitation is small sample size and low power of study. The contribution to cIMT of immunosuppressant drugs, haemodynamic changes, and type of NS has not been.

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CONFLICTS OF INTEREST

None.

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None.

ETHICAL APPROVAL

Ethical Approval has been taken from Institution Ethics Committee, Baba Raghav Das (BRD) Medical College. Signed informed consent for participation and publication of medical details were obtained from the mothers/ guardians of each patient. Confidentiality was ensured at all stages.

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