J Biochem Tech (2012) 3(4):317-321
ISSN: 0974-2328

Selected thrombosis and atherosclerosis risk factors in children with idiopathic nephrotic syndrome

Beata Bieniaś, Małgorzata Zajączkowska, Halina Borzęcka, Przemysław Sikora, Marek Majewski, Ewelina Książek, Anna Wieczorkiewicz-Płaza, Grzegorz Borzęcki

Received: 15 June 2011 / Received in revised form: 03 August 2011, Accepted: 13 August 2011, Published online: 25 February 2012

Abstract

The purpose of our study was to evaluate selected thrombosis and atherosclerosis risk factors in children with idiopathic nephrotic syndrome (INS) at three stages of the disease (I – in acute phase before steroid therapy, II – during steroid therapy after resolution of proteinuria and III – in remission after completion of steroid therapy). In all children, serum total homocysteine, lipoprotein (a), total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and triglycerides levels were measured at three stages of the disease. Plasma antithrombin III, fibrinogen and D-dimer levels were also determined. At all stages of INS, the serum t-HCY levels were similar and significantly higher than in controls. Serum lipoprotein (a) level, plasma antithrombin III, fibrinogen and D-dimer levels were significantly higher at stage I than at stages II, III and controls. In conclusion, children with INS are at high risk of thrombosis and atherosclerosis.

Keywords: Homocysteine, Lipoprotein (a), Antithrombin III, Fibrinogen, D-dimer, Nephrotic syndrome

Introduction

The idiopathic nephrotic syndrome is associated with complex disturbances in coagulation system and numerous abnormalities of lipid and homocysteine metabolism which may increase the risk of thromboembolic complications and atherosclerosis. Homocysteine is a sulfur amino acid derived from methionine during transmethylation. Remethylation to methionine in a folate- and cobalamine - dependent reaction is also possible (Welch & Loscalzo 1998; Dudman et al. 1996). Homocysteine directly injuries endothelium, induces platelets aggregation and decreases coagulation inhibitors activity (Welch & Loscalzo 1998; Dudman et al. 1996; Harker et al. 1974; Boushey et al. 1995; D'Angelo et al. 1997; Woo et al. 1997; van Guldner & Stehouwer 2000). It also generates oxidation stress and oxidation of low-density lipoprotein, increases fibrinogen level, stimulates angiogenesis and proliferation of smooth muscle cells and fibroblasts (van Guldner et al. 2000; Tsai et al. 1994; Joseph et al. 2009; Lentz et al. 2005; Harpel et al. 1992; Kronenberg 1998).

According to published data homocysteine can partially dissociate apolipoprotein (a) from lipoprotein (a) and can induce its binding to fibrin intensifying prothrombotic effect (Harpel et al. 1992; Leerink et al. 1994). Lipoprotein (a) is also recognized as a prothrombotic and atherogenic agent. The atherogenic effects of lipoprotein (a) is probably similar to those of low-density lipoprotein cholesterol (Naruszewicz et al. 1992). Its prothrombotic effects is combined with impaired fibrinolysis (Hajjar et al. 1989). Hyperhomocysteinemia in combination with decreased serum antithrombin III and increased serum lipoprotein (a), cholesterol and fibrinogen levels may contribute to high incidence of vascular diseases (Bostom et al. 1996; Berenson et al. 1998) and may also accelerate the progression of renal disease (Muntner et al. 2000).

Recently, numerous studies have demonstrated increased homocysteine levels in a variety of diseases (Bostom et al. 1996; Guven et al. 2005; Hwang et al. 2011; Sagheb et al. 2010; Ferechide & Radulescu 2009; van Guldener & Robinson 2000). The data on serum homocysteine level in patients with idiopathic nephrotic syndrome are scarce and conflicting. These data most often concern adult patients.

The purpose of our study was to evaluate selected thrombosis and atherosclerosis risk factors in children with idiopathic nephrotic syndrome at different stages of the disease.

Beata Bieniaś*, Małgorzata Zajączkowska, Halina Borzęcka, Przemysław Sikora, Marek Majewski, Ewelina Książek, Anna Wieczorkiewicz-Płaza,

Department of Pediatric Nephrology, Medical University of Lublin, Chodźki 2, 20-093 Lublin, Poland

Grzegorz Borzęcki

Department of Hygiene, Medical University of Lublin, Radziwiłłowska 11, 20-080 Lublin, Poland

* Tel: 0048 503029541, Fax: 0048 817430117
Email: beata.bienias@umlub.pl

Table 1. Concentrations of assessed parameters in patients at three stages of nephrotic syndrome and in control group

		N	Median	Range	statistical analysis
albumin (g/dl)	stage I	36	2.5	1.2-3.6	I-II p=0.0008
	stage II	36	3.3	2.3-4.4	I-III p=0.0000001
	stage III	36	4.5	3.6-5.0	II-III p=0.00002
	controls	33	4.3	4.1-5.5	I-K p=0.0000001 II-K p=0.00001 III-K p=0.35
t-HCY (umol/l)	stage I	36	12.6	9.4-20.8	I-II p=0.29
	stage II	36	12.1	9.0-18.9	I-III p=0.57
	stage III	36	12.6	9.1-16.5	II-III p=0.1
	controls	33	11.3	7.8-12.8	I-K p=0.002 II-K p=0.04 III-K p=0.04
Lp (a) (mg/dl)	stage I	36	11.3	3.1-80.2	I-II p=0.04
	stage II	36	7.5	2.4-61.2	I-III p=0.0001
	stage III	36	6.3	1.9-10.6	II-III p=0.08
	controls	33	5.2	1.7-9.0	I-K p=0.00008 II-K p=0.04 III-K p=0.06
T-CH (mg/dl)	stage I	36	276.0	157.0-702.0	I-II p=0.14
	stage II	36	259.0	142.0-424.0	I-III p=0.00003
	stage III	36	162.0	124.0-238.0	II-III p=0.01
	controls	33	160.0	98.0-185.0	I-K p=0.000001 II-K p=0.0000001 III-K p=0.46
LDL-CH (mg/dl)	stage I	36	175.9	86.8-613.0	I-II p=0.99
	stage II	36	166.5	63.0-305.0	I-III p=0.0009
	stage III	36	102.9	57.3-166.0	II-III p=0.01
	controls	33	103.0	79.0-129.8	I-K p=0.0005 II-K p=0.0005 III-K p=1.0
HDL-CH (mg/dl)	stage I	36	62.2	47.0-82.0	I-II p=0.84
	stage II	36	63.1	48.0-83.4	I-III p=0.22
	stage III	36	57.3	39.9-71.5	II-III p=0.23
	controls	33	44.5	31.0-63.0	I-K p=0.06 II-K p=0.06 III-K p=0.09
TG (mg/dl)	stage I	36	157.0	57.0-732.0	I-II p=0.49
	stage II	36	130.0	60.0-599.0	I-III p=0.0001
	stage III	36	53.0	41.0-121.0	II-III p=0.01
	controls	33	71.0	46.0-104.0	I-K p=0.000002 II-K p=0.0002 III-K p=0.13
AT III (%)	stage I	36	66.6	35.0-97.2	I-II p=0.0000001
	stage II	36	108.8	84.8-157.6	I-III p=0.0002
	stage III	36	109.0	80.0-130.0	II-III p=0.30
	controls	33	117.0	98.2-150.1	I-K p=0.0000001 II-K p=0.06 III-K p=0.18
fibrinogen (mg/dl)	stage I	36	499.0	261.0-1434.0	I-II p=0.0000001
	stage II	36	273.0	190.0-443.0	I-III p=0.0001
	stage III	36	255.0	209.0-380.0	II-III p=0.86
	controls	33	228.5	165.0-312.0	I-K p=0.0000001 II-K p=0.01 III-K p=0.29
D-dimers (ng/ml)	stage I	36	505.0	243.0-1118	I-II p=0.000001
	stage II	36	207.0	90.0-341.0	I-III p=0.0003
	stage III	36	151.5	115.0-243.0	II-III p=0.29
	controls	33	161.5	112.0-221.0	I-K p=0.0000001 II-K p=0.04 III-K p=0.85

Patients and methods

The study comprised 36 children (32 boys and 4 girls) aged 1-17 years with idiopathic nephrotic syndrome (INS) and 33 gender- and age-matched healthy controls.

In all children, serum total homocysteine (t-HCY), lipoprotein (a) (Lp (a)), total cholesterol (T-CH), low-density lipoprotein cholesterol (LDL-CH), high-density lipoprotein cholesterol (HDL-CH) and triglycerides (TG) levels were measured. Plasma antithrombin III (ATIII), fibrinogen and D-dimer levels were also determined.

The measurements were performed at three stages of the disease: I – in acute phase before steroid therapy, II - during steroid therapy after resolution of proteinuria (2-4 weeks after diagnosis of INS), III - in remission after completion of steroid therapy (6-8 months after diagnosis of INS).

Serum t-HCY levels were assessed with enzyme-linked immunosorbent assay (ELISA). Serum Lp (a) levels were measured with turbidimetric method. Serum T-CH, LDL-CH, HDL-CH and TG levels were determined using biochemical analyzer - Architekt c 8000. Plasma ATIII and fibrinogen levels were measured using Thrombolyzer Compact X whereas Mini Vidas analyzer was used to determine D-dimer level.

The statistical analysis was performed using STATISTICA 7.1. Differences between groups were assessed using Mann-Whitney test and correlation coefficients were calculated using Spearman test. A $p \leq 0.05$ was regarded as statistically significant.

Results

The results of our study are presented in Table 1. In children at stage I of INS, the median of proteinuria per 24 hours, the median of serum albumin level and the median of GFR were 173,9 ± 99 mg/kg, 2.5 ± 0.82 g/dl and 110,3 ± 27 ml/ min/1,73 m², respectively. There were no significant differences in GFR between patients at particular stages of the disease.

At all stages of INS, the serum t-HCY levels (I – 12.6 umol/l, II – 12.1 umol/l, III – 12.6 umol/l) were similar and significantly higher than in controls (11.3 umol/l) ($p<0.05$). Serum Lp (a) levels were significantly higher at stage I (11.3 mg/dl) than at stages II and III and in controls (7.5 mg/dl, 6.3 mg/dl, 5.2 mg/dl, respectively, $p<0.05$). The differences in serum Lp (a) levels between stages I and II and between stage II and controls were also statistically significant.

The serum T-CH, LDL-CH and TG levels were significantly higher at stage I (276.0, 175.9 and 157.0 mg/dl, respectively) and at stage II (259.0, 166.5, 130.0 mg/dl, respectively) than at stage III (162.0, 102.9, 53.0 mg/dl, respectively) and in controls (160.0, 103.0, 71.0 mg/dl, respectively) ($p<0.05$). The serum HDL-CH levels were

similar at all three stages of INS (I - 62.2 mg/dl, II - 63.1 mg/dl, III - 57.3 mg/dl) and in controls (44.5 mg/dl).

Plasma ATIII levels were significantly lower at stage I (66.6 %) than at stages II and III and in controls (108.8%, p=0,0000001; 109.0%, p=0,0002; 117.0%, p=0.0000001, respectively). Plasma fibrinogen levels were significantly higher at stage I (499.0 mg/dl) than at stages II and III and in controls (273.0 mg/dl, p=0.0000001; 255.0 mg/dl, p=0.0001; 228.5 mg/dl, p=0.0000001, respectively). Plasma fibrinogen levels were also significantly higher at stage II than in controls (p=0.01). Similar differences were observed in plasma D-dimer levels. At stage I plasma D-dimer levels (505.0 ng/ml) were significantly higher than at stages II and III and in controls (207.0 ng/ml, p=0.0000001; 151.5 ng/ml, p=0.0003; 161.5 ng/ml, p=0.0000001, respectively). Plasma D-dimer levels were also significantly higher at stage II than in controls (p=0.04).

Significant positive correlation between serum albumin and plasma ATIII levels was observed ($r = +0.54$, $p<0.05$) whereas correlations between levels of serum albumin and plasma fibrinogen ($r = -0.49$, $p<0.05$), plasma D-dimer ($r = -0.49$, $p<0.05$) and serum T-CH ($r = -0,64$, $p<0.05$) were significantly negative. Serum t-HCY levels showed significant positive correlation with serum Lp (a) levels ($r = +0.5$, $p<0.05$). No correlations between serum t-HCY levels and serum albumin, T-CH, LDL-H, TG levels were observed. Similarly, serum t-HCY level did not correlate with plasma antithrombin III, fibrinogen and D-dimer levels.

Discussion

The disturbances in coagulation system and lipid metabolism observed in patients with INS have been well established (Joseph et al. 2009; Wheeler & Bernard 1994; Citak et al. 2000; Singhal & Brimble 2006; Schlegel 1997; Fujita et al. 1992; 2006; Louis et al. 2003). They are due to well-known factors such as loss of albumin and anticoagulant factors (ATIII, protein C, protein S) with urine, increased number and activity of platelets, increased plasma fibrinogen and serum lipids levels, plasma volume contraction and use of diuretics and corticosteroids (Citak et al. 2000; Thabet et al. 1993; Radhakrishnan et al 1993). These disturbances give rise to higher risk of thrombosis and early atherosclerosis. In INS patients, the prevalence of thromboembolic complications vary between 1.8% to 5.3% (Fujita et al. 1992).

The development of cardiovascular diseases due to atherosclerosis in patients formerly treated for INS was also demonstrated (Kniażewska et al. 2009).

Recently, hyperhomocysteinemia is reported to be another independent risk factor for thromboembolic complications and early development of atherosclerosis. Numerous studies showed a positive correlation between hyperhomocysteinemia and risk of coronary and cerebrovascular events, peripheral vascular disease and thromboembolic complications (Boushey et al. 1995; Quere et al. 2005; Huang et al. 2000; Nygard et al. 1999; Marouf et al. 2006). An increased serum t-HCY level in adult patients with acute phase of INS was demonstrated. (Podda et al. 2007; Joven et al. 2000; Herrmann et al. 2000; Dwivedi & Sarkar 2009). Kniażewska at al. (2009) showed increased serum t-HCY levels in young patients (9 - 22 years of age) 4 to 15 years after completion of treatment for INS. In our study, we found elevated serum levels of t-HCY at all stages of INS. Our results confirm that increased serum t-HCY levels occurs not only at stage I of INS but also a lot of months after resolution of proteinuria. Similar results concerning serum t-HCY level in adult patients with nephrotic syndrome were reported by Dawivedi and Sarkar (2009). In children with INS, persistent elevated serum t-HCY levels may increase the risk of thromboembolic complications and may accelerate development of atherosclerosis. Proven causes of hyperhomocysteinemia are low serum levels of folic acid, B 6 and B12 vitamins and their administration significantly decreases serum t-HCY level (Ferechide & Radulescu 2009; Van Guldener & Robinson 2000; Podda et al. 2007; Thambyrajah et al. 2001; Rimm et al. 1998). Supplementation with these vitamins could probably be an additional therapy in patients with INS.

Previous studies demonstrated increased serum levels of Lp (a) in patients with kidney diseases and its association with the development of atherosclerosis and cardiovascular complications (Kronenberg 1998; Bostom et al. 1996; Querfeld et al. 1993; Gasevoort et al. 1994; Greiber & Wanner 1997; Kronenberg et al. 2004, Kwan et al. 2007). Other studies disclosed elevated serum Lp (a) levels in nephrotic children (Herrmann et al. 2000; Hu et al. 2009). Our studies confirmed increased serum Lp (a) levels at stage I of INS. We also observed positive correlation between serum Lp (a) and t-HCY levels. This coexistence of two thrombogenic and atherogenic factors may significantly increase the risk of acute and chronic cardiovascular diseases in children with INS.

It has been well established that in almost all patients with INS, elevated serum T-CH, LDL-CH and TG levels occur (Citak et al. 2000; Fujita et al. 2006; Thabet et al. 1993; Radhakrishnan et al. 1993; Hu et al. 2009). Serum HDL-CH level may be normal, low or high (Thabet et al. 1993; Radhakrishnan et al. 1993). Our study demonstrated increased serum T-CH, LDL-CH and TG levels at stages I and II of INS. At these stages, serum T-CH, LDL-CH and TG levels correlated negatively with serum albumin level. Children at stage III of INS had serum T-CH, LDL-CH and TG levels similar to controls. Dissimilar results were obtained by Kniażewska et al. (2009) who reported higher levels of T-CH and LDL-CH in patients 4 - 15 years after completed steroid therapy for INS. Mérouani et al. (2003) observed hyperlipidemic profile in nearly half of their nephrotic patients in remission and recommended regular monitoring of serum lipids levels, especially in those with frequent relapses. This indicates that other factors may contribute to hyperlipidemia including number of relapses of INS and perhaps genetic predisposition. However, the study by Książek et al. (2009) did not confirm the significant impact of polymorphisms of specific genes coding proteins involved in lipoprotein metabolism on persistent dyslipidemia in patients with remission of INS.

Decreased plasma level of ATIII was commonly observed in patients with INS (Lentz 2005; Citak et al. 2000). Occurrence of thromboembolic events in patients with nephrotic syndrome was demonstrated in numerous case reports (Louis et al. 2003; Kniażewska et al. 2009; Quere et al 2005; Huang et al. 2000; Balci et al 2007; Zaffanello et al. 2009). Previous studies suggested that the risk of thrombosis was significantly increased when serum albumin levels were below 2.0 g/dl and plasma ATIII levels were lower than 75% (Bernard 1988; Llach 1985). Our data confirmed significantly lower plasma ATIII levels at stage I of INS and its significant positive correlation with serum albumin levels. Hyperfibrinogenemia is often associated with INS and it is thought to be a risk factor for thromboembolic complications (Woo et al. 1997; Louis et al. 2003; Zaffanello & Franchini 2007). In our patients, increased plasma fibrinogen levels were found not only at stage I of INS but also at stage II of the disease whereas a few months after diagnosis of INS (stage III) plasma levels of fibrinogen were similar to that in healthy controls. Significant negative correlation between plasma fibrinogen and serum albumin levels was also observed.

D-dimer is a well-known molecular marker of coagulation activation. In nephrotic patients with thromboembolic complications, elevated plasma D-dimer levels were reported (Oikawa et al. 1997; Citak et al. 2000; Zaffanello et al. 2009; Morikawa et al. 2009). An increased plasma levels of D-dimer were often revealed in patients with pulmonary embolism (Huang et al. 2000). In our studies, increased plasma D-dimer levels were found at stages I and II of INS. This might confirm hypercoagulation state at these stages of the disease.

In conclusion, children with INS are at high risk of thrombosis and atherosclerosis. In children with severe hypoalbuminemia, their coagulation state should be monitored especially thoroughly and in those with thromboembolic risk factors, prophylactic treatment with anticoagulant should be initiated. An elevated serum t-HCY level persisting despite resolution of proteinuria additionally increases the risk of thromboembolic complications and early development of atherosclerosis. Therefore, in patients with INS and hyperhomocysteinemia, supplementation with folic acid, vitamin B6 and B12 in order to decrease serum homocysteine level and reduce the risk of atherosclerosis should be considered.

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