

Research Article

A study of PT, APTT, fibrinogen and urinary protein-creatinine ratio in paediatric patients with nephrotic syndrome

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Received: 20 May 2014

Accepted: 22 June 2014

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ABSTRACT

Background: Nephrotic Syndrome (NS) is very common in children. The typical laboratory finding is high urinary protein creatinine ratio. Apart from it low serum albumin, high cholesterol contribute to hyper coagulable states. Due to this the risk of thromboembolism in both arterial and venous circulation is significant in children and adults. Patients at risk for thromboembolism traditionally have to be screened by ventilation/perfusion scans and Dopplers for the definitive diagnosis of thromboembolic disease. There are several studies performed on adult nephrotic syndrome and thromboembolic events in them worldwide. We wanted to look for simple, affordable tests, that can be performed even when state of the art technology is not available, and can point towards at risk thromboembolic patients.

Methods: The study was conducted in 17 nephrotic syndrome children in active disease, 13 nephrotic syndrome children in remission and 15 healthy children as controls, all between 4-14 years age group. Study included both male and female children.

Results: Our results revealed prolonged. APTT in NS with active disease when compared to remission and control groups. High fibrinogen levels in relapse group indicated hypercoagulative state, along with routine parameters such as high cholesterol and low albumin. Both relapse and remission groups had proteinuria, with very high P/C ratio in relapse group, indicating at risk group for thromboembolic complications along with basic coagulation parameters.

Conclusion: We suggest that when there are indications of hypercoagulable state antiplatelet drugs such as a low dose aspirin 75 mg or low dose warfarin may be given as prophylactic treatment for thromboembolic disease.

Keywords: Paediatric nephrotic syndrome, Fibrinogen, PT, APTT, Protein/creatinine ratio, Thromboembolic disease

INTRODUCTION

Prevalence of nephrotic syndrome in India-age group. Thromboembolic complications are a major threat to the nephrotic syndrome patient. Pulmonary embolism and renal vein thrombosis are most grave complications of nephrotic syndrome.¹⁻⁶ Thromboembolic disease is an important complication in childhood Nephrotic Syndrome (NS) affecting about 5% of patients.⁷ A 19% incidence of abnormal ventilation/perfusion scans found in adult nephrotic syndrome patients without any clinical

evidence of pulmonary thrombosis, suggest that the real incidence of thromboembolism in nephrotic syndrome may even be higher.⁹ Patients with membranous glomerulopathy and heavy proteinuria run the highest risk.^{5,6,8} The pathophysiological mechanisms of thromboembolism in patients with nephrotic syndrome include, alterations in plasma levels of proteins involved in coagulation and fibrinolysis, enhanced platelet aggregation, low plasma albumin, hyper-viscosity and hyperlipidemia, as well as treatment with corticosteroids and diuretics.¹⁰ There are no clear factors indicating

relationship of PT, APTT and fibrinogen to protein/creatinine ratio in nephrotic syndrome children. Ambiguity and ethnic variations in all other prothrombotic factors makes it difficult to attribute them as useful diagnostic tools in thromboembolic disease.

Moreover India is a developing country with high prevalence of nephrotic syndrome children, and less number of tertiary care hospitals to diagnose nephrotic complications.

Since most of these children are treated by primary care physicians our study was conducted to facilitate early diagnosis of complications by establishing a correlation between PT, APTT, fibrinogen and protein/creatinine ratio along with serum cholesterol, serum protein and albumin concentrations.

METHODS

Thirty patients presenting with nephrotic syndrome were subjects of this study, 15 age and sex matched healthy children served as control group.

The following exclusion criteria were applied: Patients on collagen vascular disease, steroid-dependent cases, and patients on anticoagulant therapy.

Inclusion criteria were children admitted with nephrotic syndrome in relapse, out-patient review for remission.

Group-I: 17 nephrotic syndrome patients (10 males-7 females) age 4-14 years of age in relapse, before starting therapy.

Group-II: 13 nephrotic syndrome patients in remission in the age group of 4-14 years.

Controls group-III: 15 apparently healthy age and sex-matched children (9 males-6 females) 4-14 years.

All the children were clinically evaluated, for the underlying cause of nephrotic syndrome, therapy and for any manifestations of thromboembolic disease.

Laboratory investigations

The urinary protein creatinine ratio was measured on Erba-chem 5 plus semiautanalyser. Serum creatinine, total serum protein, serum albumin, cholesterol and fibrinogen were also measured by the same instrument. PT and APTT were measured by coagulometer.

RESULTS

Plasma activated partial thromboplastin time is prolonged in patients during relapse (group-I), normal during remission and in healthy controls. There is statistically significant difference between group-I and group-II with $P < 0.001$. Group-I and group III also have high statistical significance with $P < 0.001$. Between group-II and group-III, there is no significant statistical difference. Table 2 compares the three groups in respect of routine laboratory findings.

Serum creatinine was slightly lower in nephrotic patients in relapse when compared to remission and control groups, no significant statistical difference is seen between groups. Total protein and serum albumin were lower in the relapse group than the remission or control groups ($P < 0.001$) but did not differ between the remission and control groups ($P < 0.05$).

The cholesterol was higher in relapse group than either in remission or control groups ($P < 0.001$). There is no difference between remission and control groups.

The urinary protein creatinine ratio was higher in the relapse group than either in remission or control groups ($P < 0.001$), and was also higher in the remission group than the control group ($P < 0.001$). There is no statistical significance detected between study groups with regard to PT. Fibrinogen levels were higher in relapse group when compared to remission and control groups ($P < 0.001$). No statistical significance detected between remission group and controls. Cholesterol and protein/creatinine ratio positively correlated with fibrinogen and APTT, albumin and total protein have negatively correlated with fibrinogen and APTT.

Table 1: Plasma PT, APTT and fibrinogen levels in three groups.

Parameters	Ref. range	Group-I* Mean \pm SD	Group-II* Mean \pm SD)	Group-III* Mean \pm SD	P I/II	P I/III	P II/III
PT (Sec)	11-14	13.31 \pm 4.31	12.25 \pm 0.93	11.90 \pm 0.86	Not significant	Not significant	Not significant
APTT (Sec)	30-35	49.55 \pm 9.23	34.60 \pm 2.00	35.8 \pm 1.30	<0.001	<0.001	Not significant
Fibrinogen (mg%)	200-400	572.6 \pm 94.78	303 \pm 65.00	298 \pm 59	<0.001	<0.001	Not significant

*NS in relapse, NS in remission, controls represent group I, II, III respectively

Table 2: Comparison between the groups with regard to PT, APTT, fibrinogen, creatinine, total protein, serum albumin, cholesterol and urinary protein/creatinine ratio.

Parameters	Group-I* Mean ± SD	Group-II* Mean ± SD	Group-III* Mean ± SD	P I/II	P I/III	P II/III
PT	13.31 ± 4.31	12.25 ± 0.93	11.90 ± 0.86	Not significant	Not significant	Not significant
APTT	49.55 ± 9.23	34.60 ± 2.00	35.8 ± 1.30	<0.001	<0.001	Not Significant
Fibrinogen	572.6 ± 94.78	307 ± 65.00	298 ± 59	<0.001	<0.001	Not Significant
Creatinine	0.5 ± 0.10	0.6 ± 0.10	0.5 ± 0.3	Not significant	Not significant	Not significant
Total protein	3.93 ± 0.64	6.70 ± 0.52	6.98 ± 0.45	<0.001	<0.001	Not Significant
Serum albumin	1.79 ± 0.73	3.94 ± 0.58	4.1 ± 0.69	<0.001	<0.001	Not Significant
Serum cholesterol	482.5 ± 55	198 ± 30	191 ± 45	<0.001	<0.001	Not Significant
Urine protein / creatinine ratio	5.95 ± 3.72	0.35 ± 0.10	0.08 ± 0.02	<0.001	<0.001	<0.001

*NS in relapse, NS in remission, controls represent group I, II, III respectively

DISCUSSION

Thromboembolic complications are not infrequent in children with NS, and may be related to high fibrinogen, high cholesterol and low plasma albumin.³³ *In vitro* studies in patients with nephrotic syndrome have shown hyperaggregability.¹¹⁻¹⁵ This hyperaggregability has a multifactorial pathogenesis and is associated with low serum albumin, hypercholesterolemia and hyperfibrinogenemia.^{14,15}

Hypoalbuminemia increases the availability of free, normally albumin bound arachidonic acid, resulting in increased formation of the proaggregatory agent thromboxane A2 in platelets.^{12,13,16,17} Markedly elevated levels of LDL cholesterol in the nephrotic patient¹⁸ may increase *in vitro* platelet aggregation. Hypercholesterolemia also results in increased platelet aggregation.^{19,20}

Hyperfibrinogenemia invariability present in the nephrotic patient, is a third plasma factor that may increase platelet aggregability.^{25,26} A. J. Rabelink et al.³² suggested that there is a strong correlation between fibrin deposition and hyperfibrinogenemia, which becomes a main risk factor for thrombus formation. Hyperfibrinogenemia increases blood viscosity²¹ and red blood cell aggregation^{22,23} in nephrosis.

Hypoalbuminemia itself is a factor causing hypofibrinolysis.²⁴ Protein/creatinine ratio (proteinuria) is very high in nephrotic syndrome patients in relapse together with high cholesterol and low albumin levels.

There is highly significant difference in the plasma level of fibrinogen in children with relapse. Fibrinogen levels are markedly higher in children in NS relapse, than in children in remission and healthy controls.²⁷

Elevated cholesterol level is one of the feature of NS²⁸ and levels are highest during active relapse phase of the disease and disappear with resolution of the proteinuria.

Hypercholesterolemia, fibrinogen, APTT positively correlated with urine protein/creatinine ratio.

In our study APTT is prolonged in patients with NS relapse²⁹ compared with patients in remission and healthy controls, while PT in relapsed patients is not different from that of patients in remission (or) healthy controls.^{28,30,31}

CONCLUSION

Plasma fibrinogen is elevated in nephrotic syndrome patients inactive disease state. APTT is also prolonged in active state, PT being mostly normal. These fibrinogen levels and APTT are high in relapse patients with high urinary protein-creatinine ratio and high serum cholesterol.

Both fibrinogen and APTT levels when measured may detect potential cases for thrombo-embolic complications, such as pulmonary embolism and renal vein embolism (or) arterial embolism. A low dose aspirin (or) warfarin may prevent thromboembolic complications in at risk group.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the institutional ethics committee

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DOI: 10.5455/2349-3291.ijcp20140805

Cite this article as: Sujatha Rani A. A study of PT, APTT, fibrinogen and urinary protein-creatinine ratio in paediatric patients with nephrotic syndrome. *Int J Contemp Pediatr* 2014;1:89-93.