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THROMBOEMBOLIC COMPLICATIONS AND HAEMOSTASIS IN THE NEPHROTIC SYNDROME – IS THERE A DIFFERENCE BETWEEN CHILDREN AND ADULTS?

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Introduction

The high prevalence of thromboembolic complications in the nephrotic syndrome (NS) is well known [1,2]. During an approximately three year follow-up, peripheral and renal venous thrombosis and pulmonary embolism were observed in 30–40 per cent of adult NS patients [1,2] and a high prevalence has also been reported for children [3]. There is some controversy whether arterial thrombosis occurs more commonly in adult patients with NS. A high prevalence has been reported by several authors [1,2,4] but a controlled study failed to provide such evidence [5]. However, a propensity for arterial thrombosis may be difficult to demonstrate in adults because of a high baseline incidence of atherosclerosis and because of the presence of complicating factors (hypertension, smoking etc). The observation of several episodes of arterial thrombosis in children with NS prompted us to further examine haemostasis in children and adults with NS.

Patients and methods

We studied haemostasis in nine children (four male; age 5–13 years) and 32 adults (24 male; age 34 ± 11 years) with NS and renal biopsy. No patient had decreased GFR, systemic disease, ongoing thrombosis or antiplatelet medication. The histological diagnoses were: minimal change disease (four children, four adults), focal segmental glomerulosclerosis (four children, six adults), MPGN (one child, six adults) and perimembranous GN (16 adults).

Analysis: Fibrinogen gravimetrically and after Clauss [6]. Soluble fibrinogen monomer complexes (SFMC) by beta-alanin-precipitation and chromatography [6]. Antithrombin (AT) III concentration after immunoprecipitation by chromogenic assay [7].

Platelet aggregation with the stated concentrations of collagen, ADP, epinephrine and arachidonic acid. Minimal aggregatory threshold for collagen and ADP as described previously [2]. Beta-thromboglobulin (bTG) and high affinity

platelet factor 4 (Ha-PF_4) by RIA [8,9]. cAMP in platelet rich plasma (PRP) by RIA [10].

All data are reported as $\bar{X} \pm SD$. Differences between groups were calculated by Mann-Whitney's U-test. Control population refers to control individuals, age and sex matched to adult NS patients, examined at the time of the study.

Results

The prevalence of thromboembolic complications in the paediatric and adult patient group examined in this study, and in the previously described [2] total adult NS population of our hospital is reported in Table I. Among 80 cases of NS children observed over extended periods of time by one of us (O.M.), three children had arterial thrombosis: thrombosis of the right common iliac (one case), superior mesenteric (one case) and internal carotid and right posterior tibial (one case).

TABLE I. Clinical findings

	Children (n=9)	Adults (n=32)	Adults total number [6] (n=84)
Venous thrombosis	0	6	21
Renal vein thrombosis	0	2	6
Pulmonary embolism	0	3	7
Arterial thrombosis	1	1	6

TABLE II. Biochemical findings and plasmatic coagulation system

	Children (n=9)	Adults (n=32)	
Haematocrit (%)	43.9 ± 2.2	44.5 ± 3	
Albumin (g/dl)	1.89 ± 0.65	2.85 ± 0.97	
Cholesterol (mg/dl)	471 ± 210	303 ± 118	
UV_{prot} (g/24h × 1.73m²)	3.4 ± 1.46	7.8 ± 4.2	
Fibrinogen (mg/dl)	569 ± 148	416 ± 145	(200–400)+
SFMC (%)*	7.8 ± 3.4	4.8 ± 0.39	(4.80 ± 0.78)
AT III protein (%)†	56.5 ± 27	100 ± 15	(100 ± 25)
AT III activity (%)	65.0 ± 31	103 ± 18	(100 ± 25)

* SFMC as per cent of total fibrinogen

† AT III protein concentration (immunodiffusion) and activity (chromogenic assay) as per cent of normal value

\+ Normal range for adults $\bar{X} \pm SD$ in brackets

As shown in Table II, our NS children had more marked hypoalbuminaemia, hypercholesterolaemia and elevations of haematocrit than adult NS patients. More severe biochemical consequences of NS in our children are not caused by a selection artefact since comparable albumin concentrations (1.7 ± 0.6g/dl) were observed in our last 28 consecutive children with newly discovered NS.

Evidence of disseminated intravascular coagulation (DIC) in children, but not in adults, was provided by the consistent demonstration of soluble fibrin monomers. AT III concentration and activity was significantly diminished in both children and adults, but the proportion of patients with AT III <70 per cent (the risk threshold for thromboembolic complications) was higher in children (6/9) than adults (5/32). There was a highly significant correlation between albumin and AT III concentrations in children and adults.

Platelet function is reported in Table III. Elevated platelet counts, increased platelet aggregation and diminished platelet aggregation threshold was shown both in paediatric and adult NS patients. In adult patients PGE_1 stimulated cAMP concentration was significantly diminished. More marked in vivo platelet release reaction in children (but not adults) is suggested by the finding of elevated platelet indicator proteins beta-TG and HA-PF IV.

TABLE III. Platelet function

		Children (n=9)	Adults (n=32)	Adult controls (n=21)
Platelet counts ($10^3/\mu l$)		283 ± 61	281 ± 17	216 ± 53
Platelet aggregation (%max OD)				
collagen	(10^{-8} g/L)	52.5 ± 14.8	59.3 ± 12	54.5 ± 6.3
ADP	(10^{-6} M)	48.5 ± 11.3	52.7 ± 11.4	45.0 ± 6.5
epinephrine	(10^{-6} M)	24.6 ± 9.4	28.8 ± 8.2	15.9 ± 4.0*
Platelet aggregation at threshold concentration (%max OD)				
collagen	(2.5×10^{-9} g/L)	49.0 ± 29.0	52.0 ± 25.0	29.0 ± 21.0
ADP	(3.0×10^{-7} M)	16.5 ± 4.7	14.8 ± 6.7	7.0 ± 5.0
beta TG (ng/ml)		71.9 ± 46.5†	32 ± 5.3	34.7 ± 9.4
$HA\text{-}PF_4$ (ng/ml)		54.7 ± 54†	4.7 ± 58	5.8 ± 2.7
Stimulated cAMP (pmol/10^9 platelets)+			370 ± 56	489 ± 94*

$\bar{X}$

*difference between adult controls and adult NS $p < 0.05$

†difference between adult NS and children NS $p < 0.05$

+ stimulation of platelet cAMP with 5×10^{-6} M PGE_1

Conclusions

1 The occurrence of arterial thrombosis in NS children without hypertension is in agreement with the notion that NS promotes arterial as well as venous thrombosis.

2 The coagulatory consequences of NS are different in children and adults. It remains to be determined whether such difference depends on age per se or is due to more marked hypoalbuminaemia in children.

3 In children, but not in adults, soluble fibrin monomers provided evidence for intravascular coagulation.

4 Both in children and in adults with NS, marked platelet abnormalities are found but evidence for in vivo release reaction is only observed in children.

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Open Discussion

KLUTHE (Chairman) Do you really believe that there is a major difference between the behaviour of the children and the adults. May it not be only a small difference? The nephrotic syndrome in the children was more severe, you have a lower plasma volume and a greater disturbance in the coagulation system.

OERTEL That is right, children showed more severe hypoalbuminaemia, and as I pointed out this could be one of the reasons but what we found was that arterial thrombosis which will reflect a disturbance of the thrombocyte function was found to be more activated in children than adults.

KLUTHE Did you estimate the α_2 macroglobulin concentration?

OERTEL Yes but unfortunately not in all children. It was elevated, as commonly seen in the nephrotic syndrome.

KLUTHE Certainly there was a difference in α macroglobuoin between the children and the adults because of the severity of their problems.

OERTEL Yes, but it was not significantly different when we compared it with the 32 adults.

KANFER (Paris) Don't you think that elevated soluble fibrin monomer complexes could reflect localised intravascular coagulation and disseminated intravascular coagulation?

OERTEL Yes it is certainly evidence for intravascular coagulation and the better method with β-alanin precipitation and chromatography excludes artifacts due to elevated fibrinogen concentrations. But where this intravascular coagulation occurs whether in the kidney or extrarenal, I don't know.

KLUTHE In the three cases which you described with arterial thrombosis what was the severity of the nephrotic syndrome?

OERTEL The underlying disease was focal sclerosis in these patients.

BROYER (Paris) Did arterial thrombosis in your patients ever occur because of infection or volume depletion?

OERTEL In two cases there was no previous infection but in one case it was indeed. The three patients were not more volume depleted than the other cases.