Plasma Levels of Heparin Cofactor II in Nephrotic Syndrome of Children

P.		Sié ^a
B.		Meguir ^b
F.		Bouissou ^b
B.		Boneu ^a
Ph.		Barthe ^b

^aLaboratoire d'Hémostase et ^bService de Pédiatrie CI, Centre de Transfusion Sanguine, Hôpital Purpan, Toulouse, France

Dr. P. Sié, Centre Hospitalier Régional de Toulouse, Hôpital Purpan, Laboratoire d'Hémostase, F-31052 Toulouse (France)

Dear Sir,

Several studies have demonstrated a loss of anti-thrombin III (AT III) in the urine of patients with nephrotic syndrome resulting in low plasma AT III levels [1–3]. Recently, a thrombin inhibitor distinct from AT III, and called heparin cofactor II (HC II) has been characterized in human plasma. The molecular weight of HC II (65,600 daltons) is close to that of AT III and albumin. Therefore, urinary loss of HC II was possible and we performed this study to investigate this point.

Thirty-three children (2–6 years) with an idiopathic nephrotic syndrome defined as edema, hypoalbuminemia ($< 550 \mu\text{M}$) and proteinuria ($> \mu\text{g/kg/day}$) were investigated. None had renal insufficiency (serum creatinine $< 80 \mu\text{M}$). Most of them were untreated at the moment of the tests except 5 who were under corticosteroid therapy. A control group consisted of 20 normal children of the same age sent to the laboratory for preoperative coagulation tests. Blood was collected in citrated Vacutainer tubes (Becton Dickinson, ref. 606608). Citrated plasma obtained by centrifugation was stored at -70°C until assayed along with a morning urine sample. AT III was measured in plasma using a commercial amidolytic method (AT-Prest r, Stago, Asnières, France). HC II was measured in plasma using dermatan sulfate as previously described in detail [5]. In the urines, AT III and HC II were measured by electroimmunodiffusion using monospecific inhouse rabbit antisera. Calibration

This work was supported in part by grant No. 845002 from INSERM:

curves were made using a plasma pool of 30 healthy blood donors. By definition 1 unit/ml was the amount of AT III or HC II present in 1 ml of this pool. All determinations were made in duplicate.

Plasma AT III was lower in nephrotic syndrome than in controls (0.80 ± 0.24 vs. 1.02 ± 0.14 ; mean $\pm$ SD, $p < 0.01$, Mann-Whitney U test), in accordance with previous studies. Twelve children had abnormal AT III values ($< 0.70 \text{ U/min}$). In contrast, there was no difference in plasma HC II between the 2 groups (1.38 ± 0.34 vs. 1.15 ± 0.26 for nephrotic syndrome and control groups, respectively). The lower HC II level in nephrotic syndrome was 0.85 U/ml , a value within the normal range of both our reference adult and infant population. AT III-related antigen was found in the urine of 5 children but HC II was never detectable in the urine. Serum

albumin in nephrotic syndrome ranged from 180 to 550 μ M. A positive linear correlation existed between plasma AT III and serum albumin ($r = 0.64$, $p < 0.01$). In contrast, there was no relationship between plasma HC II and serum albumin nor between plasma AT III and HC II. In conclusion, this study demonstrates that HC II, unlike AT III, is not lost in the urine during severe nephrotic syndrome. This may be due to the slight differences in size or in charge between the two inhibitors [4]. The normal ratio of molar concentration of AT III over HC II in plasma is about 2.5 [4–6]. This ratio may be strongly decreased in severe nephrotic syndrome. Thus, nephrotic syndrome may constitute an appropriate phys-iopathological model for studying the effectiveness of pharmacological activators of HC II in the prevention of thrombosis, one of the major complications of this syndrome.

176

Sié/Meguirá/Bouissou/Boneu/Barthe

References

- Kauffmann, R.H.; Veltkamp, J.J.; Tilburg, N.H.V.; Van Es, L.A.: Acquired antithrombin III deficiency and thrombin in the nephrotic syndrome. *Am. J. Med.* (55:607–613 (1978).
- Jorgensen, K.A.; Stoffersen, E.: Antithrombin III and the nephrotic syndrome. *Scand. J. Haematol.* 22:442–448 (1979).
- Boneu, B.; Bouissou, F.; Abbal, M.; Sié, P.; Caranobe, C; Barthe, P.: Comparison of progressive antithrombin activity and the concentration of three thrombin inhibitors in nephrotic syndrome. *Thromb. Haemostasis* 46:623–625 (1981).
- Tollefsen, D.M.; Majerus, D.W.; Blank, M.K.: Heparin cofactor II. Purification and properties of a heparin-dependent inhibitor of thrombin in human plasma. *J. biol. Chem.* 257: 2162–2169 (1982).

Sié, P.; Dupouy, D.; Pichon, J.; Boneu, B.: Constitutional heparin cofactor II deficiency associated with recurrent thrombosis. *Lancet* ii: 414–416 (1985).

Murano, G.; Williams, L.; Miller-Andersson, M.; Aronson, D.L.; King, C: Some properties of antithrombin-III and its concentration in human plasma. *Thromb. Res.* 18: 259–262 (1980).

Book Reviews

M. Legrain, J.M. Sue, D. Durand, P. Lebon, C. Jacobs,
H. Ton That

Nephrology

Masson, New York 1987 IX+ 399 pp. ;E 12.50 ISBN 0–89352–230–9

J.-P. Grünfeld, J.-F. Bach, J. Crosnier, J.-L. Funck-Brentano,

M. H. Maxwell (eds.)

Advances in Nephrology, vol. 16

Year Book Medical Publ., Chicago 1987

XXIII + 400 pp.; E55.50

ISBN 0–8151–3585–8

This is a pleasantly printed soft-backed, pocket-size book with the essentials of nephrology in it. It is a multi-authored work with a heavy French flavor, well-translated and with some odd pieces of advice. Thus, in dysuria, it is stressed that the ‘physician (should) watch the patient urinate’. Microscopy of the urine sediment is mentioned but no photographs of the sediment are given. There are no photomicrographs of the various nephropathies in the chapter dealing with

glomerular disease which makes the book less than useful for the young physician wanting to improve his knowledge of nephrology. Similarly, in the chapter on radiology of the kidney, no computed axial tomography scans are shown, but the subject is discussed, and there is an absence of illustrations of magnetic resonance images.

All in all this book is packed with useful facts and needs a lot more illustrations to make it useful to the residents. It is not suitable for fellows in nephrology. Perhaps this dearth of appropriate illustrations can be corrected in the next edition, and then it would be well worth recommending.

This is a very recommendable publication consisting of review articles with original work in many of them. The articles are of high standard and are not solely French in origin.

It includes articles on vasopressin antagonists, renin, atrial natri-uretic peptide, antireceptor and antihormonal autoimmunity, glu-cocorticoids, and blood pressure; loop of Henle hormonal control of renal medullary function, and of the thickened ascending loop, pharmacology of loop diuretics, therapy of idiopathic membranous nephrology, Tamm-Horsfall mucoprotein, Berger's disease, autoimmunity, and glomerulonephritis, two chapters on pediatric transplantation, and two articles on erythropoietin.