

Renal vein thrombosis in nephrotic syndrome—a prospective study and review

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Summary

The incidence of renal vein thrombosis (RVT) and other thrombo-embolic phenomena was evaluated in 44 unselected patients with nephrotic syndrome. Renal vein thrombosis was demonstrated by selective renal venography in 10 patients and at post-mortem in one. Extension of the thrombus from the renal veins into the inferior vena cava was seen in 3 patients. Evidence of thrombo-embolism elsewhere in the body was seen in the form of thrombophlebitis in the lower extremities in 4 patients (9.1%), pulmonary embolism in 3 (6.8%) and myocardial infarction in one (2.3%).

Of the 11 patients with RVT, renal histology showed membranous glomerulonephritis in 3, minimal change nephritis in 5, membrano-proliferative in one and focal and diffuse proliferative glomerulonephritis in one patient each. The characteristic clinical findings such as gross haematuria and flank pain were noted in only 3 patients with RVT. No significant difference could be detected between the plasma fibrinogen, serum cholesterol, β -lipoprotein, triglycerides and phospholipid concentrations of those who showed RVT and the remainder in whom RVT was not demonstrated. The possible mechanisms involved in the pathogenesis of RVT in nephrotic syndrome are discussed.

Introduction

Although the clinical entity of renal vein thrombosis (RVT) was described by Rayer in 1840, its association with nephrotic syndrome during life was reported for the first time by Derow, Schlesinger and Savitz in 1939. Conflicting reports have appeared in the literature in recent years on the cause-and-

effect relationship of RVT with nephrotic syndrome (Kaplan, Chesney and Drummond, 1978). Whereas some authors (Pollak *et al.*, 1956; Cade *et al.*, 1977) have reported chronic RVT as a cause of nephrotic syndrome in 0.5–17.7% of adults, ample evidence has accumulated more recently which indicates that RVT is a consequence of nephrotic syndrome rather than its cause (Llach, Arieff and Massry, 1975; Llach *et al.*, 1977; Bennet, 1975; Trew *et al.*, 1978; Kauffmann *et al.*, 1978). The published data also indicate that RVT is seen more frequently in membranous and membranoproliferative glomerulonephritis than in other types (Llach *et al.*, 1977; Trew *et al.*, 1978). This prospective study was undertaken to evaluate the incidence of RVT and other thrombo-embolic phenomena in an unselected group of patients with nephrotic syndrome and their association with various types of glomerulonephritis.

Patients and methods

Forty-four patients with nephrotic syndrome admitted to the Postgraduate Institute of Medical Education and Research, Chandigarh (India), from November 1977 to December 1979 were studied. There were 32 males and 12 females. Their ages ranged from 12 to 65 years with a mean of 29.7 years. A detailed history was recorded to document any past or present history of thrombo-embolic episodes in the form of flank pain, haematuria, haemoptysis and pleuritic pain. Patients were investigated before instituting steroid or immunosuppressive therapy. Diuretics were omitted 3 days before blood volume studies.

Laboratory investigations consisted of routine urinalysis including 24-hr protein estimation, and measurement of plasma urea, serum creatinine

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proteins, lipids and blood sugar by standard techniques. Plasma fibrinogen concentration and adequacy of platelet counts were evaluated in each case. Plasma and blood volumes and red cell mass were determined by using ^{51}Cr -labelled erythrocytes (Brown, 1969). Radiological studies included chest X-ray, i.v. urogram and transfemoral selective right and left renal venography using the Seldinger technique. The latter procedure was not attempted in one seriously ill patient (Case 10). Simultaneous injection of epinephrine in the ipsilateral renal artery as recommended by Gyepes *et al.* (1969) gave an excellent visualization of the renal venous pattern.

Renal tissue was obtained by percutaneous biopsy technique in 43 patients and was studied at post-mortem in one patient (case 10). Histological sections, 3–4- μ thick, were stained with haematoxylin and eosin and periodic acid-Schiff (PAS) reagents. The histological features were graded as 0–4+ according to the severity of the glomerular basement membrane thickening, cellularity, interstitial oedema, interstitial fibrosis and margination of leucocytes. Immunofluorescence studies were carried out in selected patients.

Results

Out of 44 patients with nephrotic syndrome, RVT was detected in 11 (25%) patients. The diagnosis was established on selective renal venography in 10 patients and at post-mortem in one (Case 10).

Clinical features of the 2 groups with (I) and without (II) RVT are compared in Table 1. Flank pain and haematuria were more frequent in patients with RVT compared to those of Group II. Thromboembolic phenomena other than RVT, such as pulmonary embolism, thrombophlebitis in legs and inferior vena cava obstruction were also more commonly encountered in Group I although myocardial infarction was seen in only one patient of Group II.

Laboratory data

The mean 24-hr protein excretion and plasma fibrinogen levels (Table 2) were higher in patients of Group I but the difference was not statistically significant ($P>0.05$). No significant difference was observed between the mean total proteins and blood volume ($P>0.05$), however, the difference between the plasma volume of the 2 groups was significant ($P<0.05$). Mean serum creatinine was significantly higher in Group I ($P<0.05$).

The mean serum cholesterol, β -lipoprotein, triglycerides and phospholipids (Table 3) were significantly raised in both the groups when compared to normal ($P<0.001$) but the difference between the 2 groups was not statistically significant ($P>0.05$).

Radiological features

Selective renal venography carried out in 10 of the 11 patients of Group I, showed bilateral RVT in 3

TABLE 1. Clinical data

	Group I		Group II		P
	No.	%	No.	%	
Oedema	9	81.8	30	90.9	> 0.05
Flank pain	3	27.3	1	3.0	> 0.05
Gross haematuria	3	27.3	–	–	< 0.05
Pleural effusion	1	9.1	6	18.2	> 0.05
Hypertension	3	27.3	8	24.2	> 0.05
Myocardial infarction	0	–	1	3.0	> 0.05
Thrombophlebitis	2	18.2	2	6.1	> 0.05
Pulmonary embolism	2	18.2	1	3.0	> 0.05
Inferior vena cava involvement	3	27.3	–	–	< 0.05

Group I = 11 patients with renal vein thrombosis (RVT).

Group II = 33 patients without RVT.

TABLE 2. Laboratory data – mean values (\pm s.e. mean)

Parameters with normal values	Group I	Group II	P
24-hr proteinuria (0.05–0.15 g/l)	3.8 (1.8)	3.6 (1.8)	> 0.05
Total proteins (55–70 g/l)	41.4 (8.3)	41.7 (8.1)	> 0.05
Serum creatinine (44–135 $\mu\text{mol/l}$)	269 (3.4)	150 (7.6)	< 0.05
Fibrinogen (1.5–2.2 g/l)	3.5 (0.7)	3.1 (1.0)	> 0.05
Plasma volume (28–32 ml/kg)	46.6 (12.6)	35.4 (10.7)	< 0.05
Blood volume (70–75 ml/kg)	61.2 (20.3)	59.4 (13.4)	> 0.05

TABLE 3. Lipid profile – mean values (\pm s.e. mean)

Parameters with normal values	Group I	Group II	P
Cholesterol (3.3–5.6 mmol/l)	11.5 (3.0)	10.8 (4.1)	> 0.05
β -lipoprotein (60–70%)	80.6 (7.3)	78.2 (8.4)	> 0.05
Triglycerides (0.68–1.24 mmol/l)	1.96 (0.35)	1.81 (0.42)	> 0.05
Phospholipids (1.7–2.7 mmol/l)	4.7 (0.5)	4.4 (1.5)	> 0.05

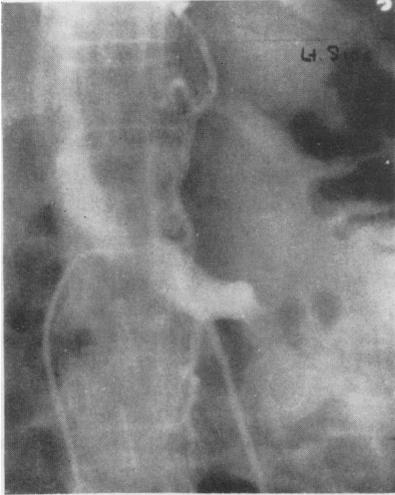


FIG. 1. Contrast study of the left renal vein showing obstruction by a thrombus and extensive collaterals. Catheter tip is seen proximal to the thrombus.

and unilateral RVT in 7 patients. Of the latter, the right renal vein was thrombosed in 4 and the left in 3 patients. Inferior vena cava was thrombosed in 3 patients. Figure 1 shows a thrombosed renal vein with collaterals as visualized by selective renal venography. Intravenous urogram showed the typical ureteral notching attributable to the dilated venous collateral vessels in one out of 10 patients with RVT. A chest X-ray suggested the presence of pulmonary infarction in 2 patients of Group I and in one patient of Group II.

Renal histology

RVT was demonstrated in 5 of 19 (26.3%) patients with minimal change glomerulonephritis; 3 of 7 (43%) with membranous nephropathy, one of 5 (20%) of both those with membrano-proliferative lesion and those with diffuse proliferative glomerulonephritis. Whereas RVT was seen in the only patient with focal proliferative glomerulonephritis in this study, it was not seen in any of the 5 with focal glomerulosclerosis.

One case showed partially canalized thrombus in one of the renal venules, suggesting the presence of

RVT. Interstitial oedema in 3 cases, infiltration and fibrosis were observed in some of the histological sections. The renal veins and the inferior vena cava were studied at post-mortem in 2 patients who died in the hospital. In one, the diagnosis was confirmed only at post-mortem. In the other, selective renal venography had shown left RVT in an earlier admission. This patient died owing to pulmonary embolism. Post-mortem confirmed the presence of thrombosis in the left renal vein, inferior vena cava (Fig. 2) and left iliac and femoral veins. Both pulmonary arteries showed evidence of embolism.

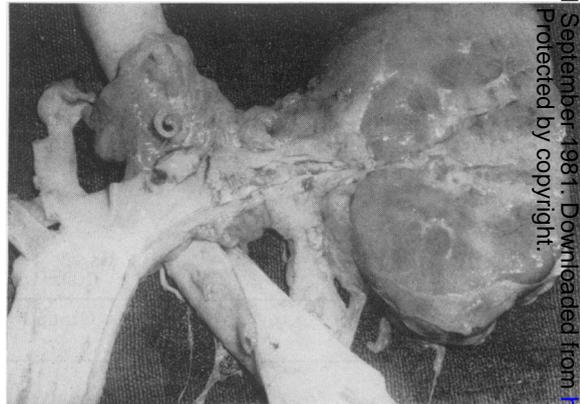


FIG. 2. Photograph showing thrombosed renal vein with collaterals as seen in a post-mortem specimen.

Discussion

In the present study, RVT was demonstrated in 25% of patients with nephrotic syndrome of varied aetiology. Although the high incidence of this complication in membranous glomerulopathy (43% observed in this study is consistent with observations recorded by others (Llach *et al.*, 1975, 1977; Bennet, 1975; Trew *et al.*, 1978; Kauffmann *et al.*, 1978), a significant number of patients with minimal change glomerulonephritis (26%) were also found to be associated with RVT in the present series. Although isolated instances of minimal change glomerulonephritis associated with RVT have been recorded (Deparis *et al.*, 1954; Balabanian, Schnetzler and

Kaloyanides, 1973; Duffy *et al.*, 1973; Kauffman *et al.*, 1978), the number of patients with minimal change nephritis included in the earlier series has been very small. Among the 48 patients of nephrotic syndrome reported by Llach *et al.* (1977), only one patient of minimal change glomerulonephritis was included. In the present study, nephrotic syndrome was due to minimal lesion glomerulonephritis in 19 patients and 5 of them showed presence of RVT.

Since Llach *et al.* (1977) had encountered RVT and other thrombo-embolic phenomena primarily in membranous or membrano-proliferative glomerulonephritis, they had hypothesized that the disease process underlying the nephrotic state might be playing a significant role in the genesis of these complications. The present data in this study do not support this view and have clearly shown that RVT may occur in a variety of nephritides and is not specifically associated with membranous or membrano-proliferative disease. The only common factor amongst these patients appeared to be the presence of a nephrotic state itself.

The characteristic histological findings associated with RVT include thickening of the basement membrane, interstitial oedema and margination of leucocytes (Pollak *et al.*, 1956; Rosenmann, Pollak and Pirani, 1968; Schreiner, 1971). In the present study, interstitial oedema was apparent in only 3 of 11 patients with RVT. In addition, one patient had a partially canalized thrombus in one of the renal venules. No other characteristic differentiating histological features were observed in those who showed RVT compared to others in whom this complication was not encountered. Similar observations have been reported by others (Llach *et al.*, 1975; Trew *et al.*, 1978).

The clinical manifestations of RVT depend upon the degree and pace of onset of the venous occlusion. The classical features of flank pain, gross haematuria, enlarged kidneys, massive proteinuria and azotaemia are present only in those in whom the venous occlusion has been sudden and complete (Harrison, Milne and Steiner, 1956; Pollak *et al.*, 1956; Pollak, Kanter and Zaltzman, 1966a). Llach *et al.* (1975) observed that the incidence of such clinical manifestation was not as frequent as previously suggested. Only 3 out of 11 patients with RVT in the present study had complained of flank pain and gross haematuria. Thus the absence of such symptoms does not exclude the occurrence of RVT. In the majority of patients, the venous occlusion is slow in onset and is incomplete and the clinical features of RVT are not easily identifiable from the primary renal disease. No significant difference was observed in the degree of proteinuria in patients with and without RVT. In 3 patients, the renal vein thrombus was observed as having ex-

tended into the inferior vena cava. These patients showed a rapid deterioration in renal function. Thrombo-embolic complications other than RVT have been reported in 10.8–23% of cases of nephrotic syndrome (Llach *et al.*, 1977; Cade *et al.*, 1977; Kauffman *et al.*, 1978).

Pyelographic features in RVT consist of notching or scalloping of the ureters and enlargement of the kidneys (Chait *et al.*, 1968; Mulhern *et al.*, 1975). Only one patient with RVT had such radiological findings. The diagnosis of RVT can be established during life only by selective renal venography. The diagnostic criteria include (i) the absence of streamlining at the site of entry of the renal vein into the inferior vena cava, (ii) non-filling of part of the main renal vein or segmental branches, (iii) constant radiolucency surrounded by contrast, and (iv) presence of collaterals (Mulhern *et al.*, 1975). Venous collaterals as well as peripheral intra-renal veins can be better visualized by adrenaline-assisted renal venography (Gyepes *et al.*, 1969).

The exact mechanism of occurrence of RVT in nephrotic patients is not clear. Higher concentrations of factors V, VII, VIII and X, accelerated generation of thromboplastin, activation of Hageman factor, thrombocytosis and increased production of fibrinogen by liver under conditions of proteinuria or hypoproteinaemia have been implicated as causing hypercoagulability (Kendall, Lohmann and Dossetor, 1971; Thomson, Forbes and Prentice, 1974). Anti-thrombin III deficiency has recently been reported as an important factor for the increased incidence of thrombosis and thrombo-embolic episodes in patients with nephrotic syndrome (Kauffmann *et al.*, 1978). Although elevated concentrations of fibrinogen were observed in the present study, the concentrations were not significantly different in those who showed and those who did not show RVT. Reduction in blood volume has also been incriminated for the genesis of RVT in nephrotic state (Trew *et al.*, 1978) but no significant difference was found between the 2 groups in the present study. Further studies are required for elucidation of the factors which lead to increased frequency of venous thrombosis in nephrotic syndrome.

References

- BALABANIAN, M.B., SCHNETZLER, D.E. & KALOYANIDES, G.J. (1973) Nephrotic syndrome, renal vein thrombosis and renal failure. *American Journal of Medicine*, **54**, 768.
- BENNET, W.W. (1975) Renal vein thrombosis in nephrotic syndrome. *Annals of Internal Medicine*, **83**, 577.
- BROWN, D.F. (1969) Blood lipids and lipoproteins in atherogenesis. *American Journal of Medicine*, **46**, 691.
- CADE, J.R., SPOONER, G., JUNCOS, L., FULLER, T., TARRANT, D., RAULERSON, D., MAHONEY, J., PICKERING, M., GRUBB, W. & MARBURY, T. (1977) Chronic renal vein thrombosis. *American Journal of Medicine*, **63**, 387.

- CHAIT, A., STOANE, L., MOSKOWITZ, H. & MELLINS, H.Z. (1968) Renal vein thrombosis. *Radiology*, **90**, 886.
- DEPARIS, M., ACQUIER, L., CANIVET, J., LEVILLAIN, R. & LISSAC, J. (1954) Thrombose des veines rénales et néphrose lipidique. *Presse médicale*, **2**, 1363.
- DEROW, H.A., SCHLESINGER, M.J. & SAVITZ, H.A. (1939) Chronic progressive occlusion of inferior vena cava and the renal and portal veins. *Archives of Internal Medicine*, **63**, 626.
- DUFFY, J.L., LETTERI, J., CLINQUE, T., HSU, P.P., MOLHO, L. & CHURG, J. (1973) Renal vein thrombosis and the nephrotic syndrome. *American Journal of Medicine*, **54**, 633.
- GYEPES, M.T., DESILETS, D.T., GRAY, R.K. & KATZ, R.M. (1969) Epinephrine-assisted renal venography in renal vein thrombosis: report of two adolescents with nephrotic syndrome. *Radiology*, **93**, 793.
- HARRISON, C.V., MILNE, M.D. & STEINER, R.E. (1956) Clinical aspect of renal vein thrombosis. *Quarterly Journal of Medicine*, **25**, 285.
- KAPLAN, B.S., CHESNEY, R.W. & DRUMMOND, K.N. (1978) The nephrotic syndrome and renal vein thrombosis. *American Journal of Diseases of Children*, **132**, 367.
- KAUFFMANN, R.H., VELKAMP, J.J., VAN TILBURG, N.H. & VANES, L.A. (1978) Acquired anti-thrombin III deficiency and thrombosis in the nephrotic syndrome. *American Journal of Medicine*, **65**, 607.
- KENDALL, A.G., LOHMANN, R.C. & DOSSETOR, J.B. (1971) Nephrotic syndrome: a hypercoagulable state. *Archives of Internal Medicine*, **127**, 1021.
- LLACH, F., ARIEFF, A.I. & MASSRY, S.G. (1975) Renal vein thrombosis and nephrotic syndrome: a prospective study of 36 adult patients. *Annals of Internal Medicine*, **83**, 8.
- LLACH, F., KOFFLER, A., FLINCK, E. & MASSRY, S.G. (1977) On the incidence of renal vein thrombosis in the nephrotic syndrome. *Archives of Internal Medicine*, **137**, 333.
- MULHERN, C.B., ARGER, P.H., MILLER, W.T. & CHAIT, A. (1975) The specificity of renal vein thrombosis. *American Journal of Roentgenology*, **125**, 291.
- POLLAK, V.E., KANTER, A. & ZALTZMAN, S. (1966a) Renal vein thrombosis. *Postgraduate Medicine*, **40**, 282.
- POLLAK, V.E., KARK, R.M., PIRANI, C.L., SHAFTER, H.A. & MEUHRCKE, R.C. (1956) Renal vein thrombosis and the nephrotic syndrome. *American Journal of Medicine*, **21**, 496.
- POLLAK, V.E., PIRANI, C.L., SESKIND, C. & GRIEFEL, E. (1966b) Bilateral renal vein thrombosis: clinical and electron micrographical studies of a case with complete recovery after anticoagulant therapy. *Annals of Internal Medicine*, **65**, 1056.
- RAYER, P.F.O. (1840) *Traité des Maladies des Veines*, p. 269. Baillière, Paris.
- ROSENMAN, E., POLLAK, V.E. & PIRANI, C.L. (1968) Renal vein thrombosis in the adult: a clinical and pathological study based on renal biopsies. *Medicine*, **47**, 269.
- SCHREINER, G.E. (1971) The nephrotic syndrome. In *Diseases of the Kidney* (Ed by Strauss, M.B. & Welt, L.G.), 2nd edn, p. 576. Little, Brown & Co., Boston.
- THOMSON, C., FORBES, C.D. & PRENTICE, C.R.M. (1974) Changes in blood coagulation and fibrinolysis in the nephrotic syndrome. *Quarterly Journal of Medicine*, **43**, 399.
- TREW, R.A., BIAVA, C.G., JACOBS, R.P. & HOPPER, J. (1978) Renal vein thrombosis in membranous glomerulonephropathy: incidence and association. *Medicine*, **57**, 69.