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Proteinuria and other renal functions in Wilson's disease

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Abstract. Renal lesions have repeatedly been described in Wilson's disease (WD). We investigated the excretion of total protein, albumin, low (LMW) and high molecular weight (HMW) proteins, *N*-acetyl-β-D-glucosaminidase (NAG), and calcium, as well as creatinine clearance, in 24-h urine samples of 41 patients with WD aged 6–37 (mean 17) years who had been treated for a period of 0–15 (mean 4.5) years with D-penicillamine (900 mg/day). The amount of all protein excreted was significantly increased compared with controls, 39% of patients presenting with total proteinuria more than two standard deviations from the mean of controls. The changes in protein excretion depended on the duration of treatment. LMW proteinuria was elevated almost exclusively in the first 2 years after the start of treatment, indicating early tubular damage. This is supported by an initially high excretion of β_2-microglobulin, NAG, and calcium. Increased excretion of HMW proteins, including albumin, persisted over longer periods, which suggests glomerular injury in some patients, possibly related to the use of D-penicillamine. Creatinine clearance remained roughly within normal limits. We propose that renal function should regularly be checked in patients with WD.

Key words: Wilson's disease – Hepatolenticular degeneration – Proteinuria – Tubular disorder – Calciuria – Copper metabolism

Introduction

Wilson's disease (WD) or hepatolenticular degeneration is an autosomal recessive error of copper metabolism transmitted on chromosome 13 [1, 2]. It is generally accepted that the clinical and pathological manifestations of WD are due to an excessive accumulation of copper in liver, brain, cornea, kidneys, and other tissues. Renal symptoms are a presenting feature in only about 1% of patients [3], usually as renal insufficiency with fulminant hepatic failure and hemolysis [2]. Several studies have demonstrated that minor alterations in renal function and morphology are common in untreated patients with WD [4, 5]. However, only one study has comprehensively assessed tubular and glomerular function in untreated and treated patients with WD [6]. Proteinuria has rarely been investigated in detail [6, 7].

In 1956 Walshe introduced penicillamine in the treatment of WD. By its cupriuretic action, this drug is able to deplete body copper stores and to alleviate the clinical manifestations of WD. Concomitantly, glomerular and tubular functions normalize or are at least improved [6, 8, 9]. In rare cases, however, penicillamine may have a nephrotoxic action in WD [10], although this effect has mainly been described in other disorders such as rheumatoid arthritis [11].

The aim of the present study was to investigate selected glomerular and tubular functions in young patients with WD treated with D-penicillamine for up to 15 years. As indices we used, besides glomerular filtration rate (GFR), the excretion of low (LMW) and high molecular weight (HMW) proteins, *N*-acetyl-β-D-glucosaminidase (NAG) as a marker enzyme of tubular function, and calciuria. In some patients the tests were repeated to study individual long-term changes.

Patients and methods

From 1969 to 1994 we observed 105 patients fulfilling the criteria of WD as the most frequent non-viral chronic liver disease in children [12, 13]. Only 4 of these showed overt renal disease: (1) a 14-year-old girl who 8 months after the start of D-penicillamine treatment developed nephrotic syndrome, macroscopic hematuria, hypertension, and renal failure (serum creatinine up to 3.7 g/dl), associated with a palmar rash, anemia, and thrombocytopenia; renal biopsy revealed diffuse mesangioproliferative glomerulonephritis with mesangial and periph-

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Table 1. Urinary excretion of proteins, N-acetyl-β-D-glucosaminidase (NAG), calcium, and creatinine clearance in Wilson's disease[a]

	Patients				Controls			
	n	Mean (± SD)	Median (range)	% patients >2 SD of mean of controls	*n*	Mean (± SD)	Median (range)	*P* <
Total proteins (mg/m² per hour)	41	4.03 (±2.44)	3.70 (1.1–13.4)	39%	80	1.77 (±1.00)	1.51 (0.29–5.1)	0.0001
Albumin (RIA) (μg/m² per min)	18	8.14 (±7.13)	5.89 (0.35–19.4)	33%	68	3.55 (±3.10)	2.60 (0.06–15.2)	0.0001
Albumin (SDS-PAGE) (mg/m² per hour)	40	2.10 (±1.46)	1.92 (0.7–6.8)	22%	63	1.06 (±0.80)	0.79 (0.10–4.10)	0.0001
LMW proteins (mg/m² per hour)	40	1.23 (±1.27)	0.86 (0–5.5)	25%	63	0.46 (±0.36)	0.38 (0–2.0)	0.0001
HMW proteins (mg/m² per hour)	40	0.76 (±0.64)	0.59 (0–2.53)	22%	63	0.38 (±0.37)	0.28 (0–1.8)	0.0001
β_2-microglobulin (μg/m² per hour)	27	4.95 (±6.39)	2.91 (0.1–32)	15%	80	2.60 (±2.10)	2.08 (0.5–15.4)	0.004
NAG (U/g creatinine)	27	4.73 (±4.51)	3.82 (0.75–18.4)	22%	52	3.90 (±1.53)	3.55 (1.3–8.9)	0.08
Calcium excretion (μmol/kg per 24 h)	17	74 (±39)	68 (13–180)	18%		65 (±25)		NS
Creatinine clearance (ml/min per 1.73 m²)	40	107 (±25)	100 (65–174)					

SD, Standard deviation; RIA, radioimmunoassay; SDS-PAGE, sodium dodecyl sulfate polyacrylamide gel electrophoresis; LMW, low molecular weight; HMW, high molecular weight; NS, not significant

[a] For calculation only the first urine specimen of each patient was used

eral IgM and complement deposits; after withdrawal of D-penicillamine and replacement by zinc therapy and transient administration of prednisone, all renal symptoms except microhematuria disappeared 9 months after the acute episode; (2) a 12-year-old girl presenting with proteinuria and microscopic hematuria who was lost to follow-up; (3) a young adult man with isolated persistent proteinuria over many years (around 1 g/dl per 24 h) and normal renal function; (4) a boy admitted for acute hemolysis, liver and renal failure who died within a few days despite intensive treatment. All these patients were excluded from the investigation described below.

Forty-one patients (21 females) were available for the present study. The main presenting symptoms were chronic hepatitis (15 cases), liver cirrhosis (6), neurological manifestations (6), hemolysis (1), and hemorrhage (1); 12 patients were in a presymptomatic stage. None of 41 patients had renal disease. The mean age at the time of diagnosis was 13 (range 4–31) years; 5 patients were over 20 years. All patients were treated with D-penicillamine from the time of diagnosis at a uniform dose of 300 mg/day, given three times daily, independent of body size. The duration of D-penicillamine treatment was up to 1 year in 14 patients, 1–2 years in 5 patients, 2–5 years in 5 patients, 5–10 years in 15 patients, and >10 years in 2 patients (mean 4.5 years).

At the time of the present investigation the mean age was 17 (range 6–37) years. Serum creatinine was always in the normal range. In all patients at least one 24-h urine specimen was collected and stored at –20° C for determination of different proteins, NAG, calcium, and creatinine clearance (C_{Cr}). In 10 patients the investigation was repeated after 3 months to 12 years. The proteinuria and enzymuria were compared with 80 controls (43 females) aged 6–18 (mean 10) years [14]. Coomassie brilliant blue (Biorad) was used to measure total protein [15]. For determination of LMW and HMW proteins, we used sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) after concentration of the urine by dialysis [16, 17]. We used 0.48-mm-thick slab gels with an exponential polyacrylamide gradient from 4.0% to 22.5%, according to Goerg et al. [16], and the Laemmli buffer system. The gels were stained with Serva blue G 250 (Serva, Heidelberg, Germany) and evaluated semi-quantitatively by densitometry using an Ultrascan laser densitometer and a recording integrator (LKB, Munich, Germany). This procedure allowed separation of LMW proteins, HMW proteins, and the albumin fraction, expressed as a percentage of the total urinary protein. Albumin was also determined by radioimmunoassay (Pharmacia), β_2-microglobulin by enzyme-linked immunosorbent assay (Pharmacia), and NAG by a colorimetric method. Calcium and creatinine were measured by standard methods.

Statistics. Fisher's exact test was used for assessing the significance of differences in proteinuria and NAG excretion between patients and controls.

Results

The total protein, albumin, LMW and HMW proteins, and β_2-microglobulin excreted in urine was about 2–3 times higher in patients than in controls (Table 1). Total protein

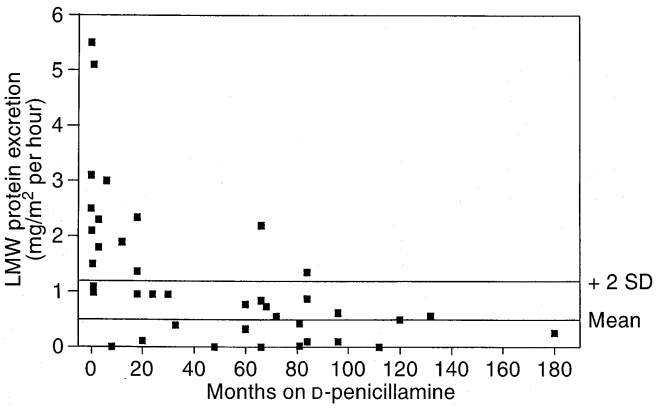

Fig. 1. Urinary excretion of low molecular weight (*LMW*) proteins in 40 patients with Wilson's disease (WD) on D-penicillamine treatment for 0–180 months. In patients tested repeatedly, only the first urine specimen obtained is represented. The two *horizontal lines* represent the mean and mean plus two standard deviations (*SD*) in controls

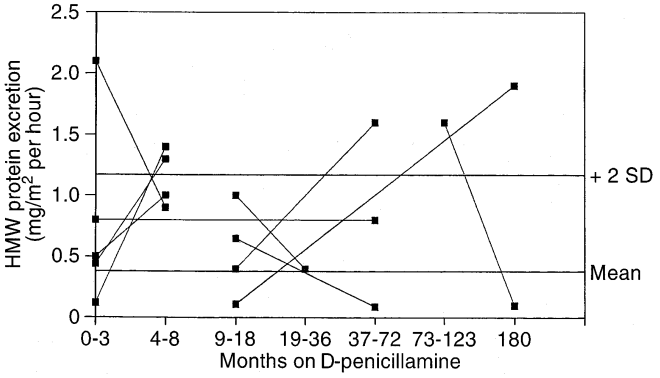

Fig. 2. Serial measurements of high molecular weight (*HMW*) proteinuria in 10 patients with WD related to the duration of D-penicillamine treatment

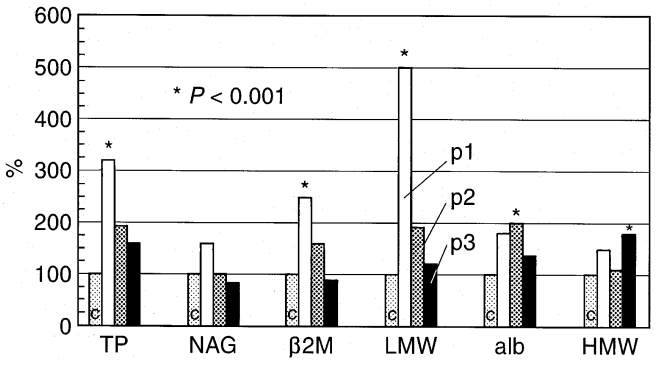

Fig. 3. Excretion of total proteins (*TP*), N-acetyl-β-D-glucosaminidase (*NAG*), β_2-microglobulin (β_2M), LMW proteins, HMW proteins, and albumin (*alb*) in different time periods after the start of D-penicillamine treatment, represented by three columns: p1, 1st year; p2, 2–4 years; p3, 5–15 years. Only the first urine specimen obtained is represented. The mean data for each period are expressed as percentage of mean control values (*c*)

excretion was above the upper normal limit (2 SD above mean) in 39% patients; all but 2 patients had values below 6 mg/m² per hour, the exceptions had total proteinuria of 13.5 mg/m² per hour; shortly after the start of D-penicillamine.

When related to the duration of D-penicillamine treatment, the proportion of patients with pathologically high values of total proteinuria, albuminuria, and LMW proteinuria declined with time. This change was most marked with LMW proteins: whilst 12 of 18 patients assessed in the first 2 years after the start of therapy had an increased LMW proteinuria, the same was found in only 2 of 22 patients assessed later (Fig. 1). In contrast, increased HMW protein and albumin excretion were more evenly distributed over the years on treatment. Only 2 of 18 patients assessed in the first 2 years had increased HMW proteinuria compared with 6 of 22 followed for a longer period. Comparable trends were also observed in individual patients tested repeatedly. Of 10 patients with two measurements by SDS-PAGE, 8 showed declining amounts of LMW protein in urine with time (not shown). In contrast, HMW proteinuria increased in 5 of 10 patients tested (Fig. 2) and albuminuria increased in 8 of 10 patients (not shown). In 3 of 4 patients, β_2-microglobulin levels were increased within 3 months of the start of therapy; in 2 of these they later became normal.

Although the excretion of NAG was higher in patients than in controls, the difference was not significant (Table 1). All 6 patients with elevated NAG excretion were observed during the first 6 months after the start of treatment. Of 10 patients tested repeatedly, 2 showed a fall of NAG excretion within the normal range.

Calcium excretion was above normal (>90 μmol/kg per day) in 3 of 17 patients (in 2 during the first 3 months). In a further 3 patients, calciuria was just at the upper normal limit. C_{Cr} was above 75 ml/min per 1.73 m² in all but 4 patients, the lowest value being 65 ml/min per 1.73 m².

In Fig. 3 the mean protein and NAG excretion is represented as a percentage of mean normal values according to the duration of D-penicillamine therapy. In the 1st year the excretion of the tubular markers NAG, β_2-microglobulin, and especially LMW proteins, as well as total proteins, was higher compared with subsequent periods. In contrast, the mean maximum excretion of albumin and HMW proteins occurred after the 1st year of treatment.

Discussion

Previous investigations demonstrated that *tubular function* in untreated patients with WD is more markedly affected than glomerular function. In different studies, increased excretion of amino acids [6, 9, 18, 19], oligopeptides, glucose, uric acid [4], phosphate [9], calcium [20], and para-aminohippurate [6] were observed. In addition, defects in urinary acidification [4, 6, 8] were reported. Rarely a severe generalized Fanconi syndrome was observed [21]. Some authors described hematuria [6] and a mild reduction in GFR and renal plasma flow which, similar to the tubular dysfunction, was usually reversible after treatment with D-penicillamine [4, 6, 22]. Early studies had failed to show significant pathoanatomical changes in kidney biopsies, but Wolff [23] described five autopsy cases with tubular necrosis and degeneration.

The *pathogenesis* of kidney lesions in WD has been related to the increased copper stores. Tubular dysfunction in WD seems to be associated with the amount of copper deposited in body tissues and specifically in the tubular epithelium [10, 22, 24, 25]. Structural alterations of mitochondria found in proximal tubular cells of patients with WD [26] indicate a disturbance of renal energy metabolism. The nephrotoxic action of copper was also demonstrated in mice and rats where it led to necrosis of proximal tubules and other renal lesions [23, 24, 27, 28].

Proteinuria has rarely been studied in WD. In a long-term study of 20 patients treated with D-penicillamine, Lange [29] failed to find any patients with increased proteinuria or nephrotic syndrome. Leu et al. [6] reported that five of seven untreated patients aged 14–48 years excreted increased amounts of protein (mean 199 mg/24 h vs. 23 mg/24 h in controls), whilst proteinuria was significantly lower under treatment with D-penicillamine (mean 48 mg/24 h);

the analytical method used was not indicated. Peterson et al. [7] described three patients with WD in whom the excretion of β_2-microglobulin was higher than that of albumin or total protein. Increased total proteinuria (0.3–1 g/24 h) was also reported more recently in 3 of 37 WD patients [30].

Our study demonstrates that increased proteinuria persists in about a third of all patients treated with D-penicillamine, although it rarely reaches a high level. The application of SDS-PAGE revealed a different time course for LMW and HMW proteinuria: *LMW proteins* were excreted in excess of control values in two-thirds of patients examined in the first 2 years after the start of D-penicillamine treatment, but serial determinations showed declining amounts with time. Elevated excretion of other tubular markers, i.e., β_2-microglobulin and NAG, was also restricted to the initial period of drug therapy. These findings are in agreement with earlier observations that tubular function usually revert to normal within 2 years of D-penicillamine therapy [6, 8]. During this period the tubular lesions caused by copper deposition are also regressing [10].

In contrast to LMW proteinuria, we found that albuminuria and *HMW proteinuria* are persistently increased in some patients. This might be interpreted as a mild nephrotoxic effect of D-penicillamine. Our observations may be related to the rare WD patients who developed massive proteinuria or nephrotic syndrome, with or without rash, many months or years after the start of treatment of DL-penicillamine, possibly due to an immunogenic action of this drug [31–33]. With the introduction of the D-isomer of penicillamine, such reaction became exceptional [34, 35]. However, at least 1 of our patients with proteinuria appears to have suffered from an adverse effect of this drug, because she rapidly recovered after its withdrawal.

From our studies it appears possible that in WD long-term administration of D-penicillamine is able to induce a minor degree of glomerular proteinuria in the absence of more severe renal or systemic manifestations. However, it cannot be excluded that persistent proteinuria in long-standing WD is related to the condition itself.

The *GFR* remained within the normal range in almost all our patients. This needs to be confirmed by more accurate measurement, but we agree with the observations of Leu et al. [6] who rarely found a small decrease of inulin clearance in treated WD patients. A reduced GFR may be explained by an effect of D-penicillamine on the molecular structure of the glomerular basement membrane, i.e., an inhibition of enzymes required for collagen synthesis [36]. In animal experiments, however, only very high doses of D-penicillamine (>450 mg/kg) were able to induce severe albuminuria and increased NAG excretion [37].

Hypercalciuria was an occasional finding in our patients with WD, restricted to the early phase of treatment and never accompanied by nephrolithiasis or nephrocalcinosis. Some studies reviewed by Hoppe et al. [20] have reported a high incidence of hypercalciuria and kidney stones in WD. High calcium excretion may [6] or may not [20] decrease on D-penicillamine treatment.

In conclusion, the increased excretion of tubular proteins in WD was confined mainly to the first 2 years of D-penicillamine treatment, which suggests a close relationship to the primary metabolic disorder rather than to the drug. In contrast, HMW proteinuria and albuminuria, as markers of glomerular damage, persisted in some patients for many years after the start of D-penicillamine therapy which, however, does not prove an etiological role of the drug. We cannot decide whether the low persistent HMW proteinuria is due to a toxic action of D-penicillamine, suggested by the rare cases of nephrotic syndrome. Such patients might benefit from a switch to other drugs (e.g., zinc or trientine). The normal GFR observed in almost all our patients on long-term D-penicillamine treatment indicates that this regimen is usually well tolerated by the kidney. The nephrologist should, however, be aware of the rare patient with WD who manifests as acute renal failure related to a hemolytic crisis and liver failure [33, 38], and who may profit from liver transplantation [4].

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References

1. Danks DM (1991) Disorders of copper transport. In: Scriver CR, Beaudet AL, Sly WS, Valle D (eds) The metabolic basis of inherited disease, 6th edn. McGraw Hill, New York, pp 1411–1431
2. Sokol RJ (1994) Wilson's disease and Indian childhood cirrhosis. In: Suchy FJ (ed) Liver disease in children. Mosby, St. Louis, pp 747–772
3. Scheinberg IH, Sternlieb I (1984) Wilson's disease. Saunders, Philadelphia, pp 1–171
4. Bearn AG, Yü TF, Gutman AB (1957) Renal function in Wilson's disease. J Clin Invest 36: 1107–1114
5. Huang CC, Chu NS (1992) Wilson's disease: clinical analysis of 71 cases and comparison with previous Chinese series. J Formos Med Assoc 91: 502–507
6. Leu ML, Strickland GT, Gutman RA (1970) Renal function in Wilson's disease: response to penicillamine therapy. Am J Med Sci 260: 381–398
7. Peterson PA, Evrin PE, Berggard I (1969) Differentiation of glomerular, tubular and normal proteinuria: determination of urinary excretion of β_2-microglobulin, albumin, and total protein. J Clin Invest 48: 1189–1198
8. Walshe JM (1968) Effect of penicillamine on failure of renal acidification in Wilson's disease. Lancet I: 775–778
9. Schonheyder F, Gregersen G, Hansen HE, Skov PE (1971) Renal clearances of different aminoacids in Wilson's disease before and after treatment with penicillamine. Acta Med Scand 190: 395–399
10. Elsas LJ, Hayslett JP, Spargo BH, Durant JL, Rosenberg LE (1971) Wilson's disease with reversible renal tubular dysfunction. Correlation with proximal tubular ultrastructure. Ann Intern Med 75: 427–433
11. Hall CL, Jawad D, Harrison PR, Mackenzie JC, Bacon PA, Klouda PT (1988) Natural course of penicillamine nephropathy: a long term study of 33 patients. B M J 296: 1083–1086
12. Feist D (1982) Die Wilson'sche Krankheit als hepatologisches Problem. Int Welt 5: 213–218
13. Feist D (1995) Neue Aspekte der Hepatologie im Kindesalter. Sozialpädiatrie 17: 276–279
14. Wartha R, Schärer K, Wollanka H, Schmidt H, Hasslacher C (1989) Patterns of proteinuria and urinary enzyme excretion in children and adolescents with diabetes mellitus. Pediatr Adolesc Endocrinol 18: 133–148
15. Bradford MM (1976) A rapid and sensitive method for quantitation of microgram quantities of proteins utilizing the principle of protein dye binding. Anal Biochem 72: 248–254

16. Goerg A, Postel W, Westermeier R, Righetti PG, Ek C (1982) One and two dimensional electrophoresis performed horizontally in ultrathin SDS pore-gradient gels. LKB application note 320. Bromma, Sweden
17. Ries M, Schärer K, Wartha R, Schmidt H, Gekle D (1991) Microheterogeneity of urinary albumin and tubular proteinuria in juvenile diabetes mellitus. Pediatr Nephrol 5: 582–586
18. Uzmann LL, Denny-Brown D (1948) Aminoaciduria in hepatolenticular degeneration (Wilson's disease). Am J Med Sci 260: 381–398
19. Bickel H, Neale FC, Hall G (1957) A clinical and biochemical study of hepatolenticular degeneration (Wilson's disease). Q J Med 26: 527–558
20. Hoppe B, Neuhaus T, Superti-Furga A, Forster I, Leumann E (1993) Hypercalciuria and nephrocalcinosis, a feature of Wilson's disease. Nephron 65: 460–462
21. Morgan HG, Stewart WK, Lome KG, Stowers JM, Johnstone JH (1962) Wilson's disease and the Fanconi syndrome. Q J Med 31: 361–384
22. Walshe JM (1969) Management of penicillamine nephropathy in Wilson's disease: a new chelating agent. Lancet II: 1401
23. Wolff SM (1964) Renal lesions in Wilson's disease. Lancet I: 843–845
24. Yoshitoshi Y, Oda T, Yamane Y, Nagase M, Mori K, Shikata T (1968) Renal lesions in Wilson's disease. Birth Defects 4: 104–108
25. Jaffe IA, Treiser G, Suzuki Y, Ehrenreich T (1968) Nephropathy induced by D-penicillamine. Ann Intern Med 69: 549–555
26. Reynolds ES, Tannen RL, Tyler HR (1966) The renal lesion in Wilson's disease. Am J Med 40: 518–527
27. Vogel FS (1960) Nephrotoxic properties of copper and experimental conditions in mice. Am J Pathol 36: 699–711
28. Hosovski E, Sunderic D, Sindjic M (1990) Functional and histologic changes in the kidney in copper poisoning in rats (in Serbo-Croatian). Srp Arh Celok Lek 118: 445–449
29. Lange (1967) Die Langzeitbehandlung des Morbus Wilson mit D-Penicillamin. Dtsch Med Wochenschr 92: 1657–1662
30. Lau JYN, Lai CL, Wu PC, Pan HYM, Lin HJ, Todd D (1990) Wilson's disease: 35 years experience. Q J M 278: 597–605
31. Adams DA, Goldman R, Maxwell MH, Latta H (1964) Nephrotic syndrome associated with penicillamine therapy of Wilson's disease. Am J Med 36: 330–336
32. Sternlieb I, Scheinberg IH (1964) Penicillamine therapy for hepatolenticular degeneration. J Am Med Assoc 189: 748–754
33. Karp M, Lurie M, Yonis Z (1966) Nephrotic syndrome in the course of treatment of Wilson's disease with DL-penicillamine. Arch Dis Child 41: 684–688
34. Castellvi Suana JM, Xiol-Quingles X, Castellote Alonso J, Guardiola-Capon J (1993) Sindrome nefrosico secondaria a d-penicillamina en la enfermedad de Wilson. Rev Clin Esp 193: 343–344
35. Suda M, Kubota J, Yamaguchi F, Fujioka Y, Saito Y, Aoki T (1993) A study of trientine therapy in Wilson's disease with neurological symptoms. No To Hattatsu 25: 429–434
36. Nimni ME (1977) Mechanism of inhibition of collagen cross-linking by penicillamine. Proc R Soc Med 70 [Suppl 3]: 65
37. Khalil-Manesh F, Price RG (1983) Effect of D-penicillamine on glomerular basement membrane, urinary *N*-acetyl-β-D-glucosaminidase and protein excretion in rats. Toxicology 26: 325–334
38. Herra SA, Hevia FJ, Vargas M, Schosinsky K (1990) Fulminant Wilson's disease in Costa Rica. Clinicopathological study of 7 cases (in Spanish). G E N 44: 9–14

Literature abstract

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Familial glomerulopathy with giant fibrillar (fibronectin-positive) deposits: 15-year follow-up in a large kindred

O. Gemperle, J. Neuweiler, F. W. Reutter, F. Hildebrandt, and R. Krapf

A 15-year clinical follow-up is reported for a familial glomerulopathy characterized on light microscopy by the glomerular deposition of giant fibrillary deposits (Virchows Arch A Pathol Anat Histol 388: 313–326, 1980). On electron microscopy, the deposits consist of randomly oriented fibrils (12 to 16 nm in width and 120 to 170 nm in length). These deposits show positive immunoreactivity for fibronectin. One hundred fifty-seven of 197 family members within five generations were investigated. The disease is characterized by the occurrence of albuminuria in the third to fourth decades of life and slow progression to end-stage renal disease over a period of 15 to 20 years with the occurrence of generalized distal tubular acidosis (renal tubular acidosis type IV), hypertension, and the nephrotic syndrome. The frequent occurrence of otherwise unexplained microalbuminuria in young individuals of generations IV and V could be indicative of incipient glomerular disease. In one affected male individual and in his unaffected sister, renal cell carcinoma was diagnosed, raising the possibility that this familial glomerulopathy might be associated with an increased risk to develop renal cell cancer by direct or indirect (associated genetic predisposition) mechanisms. The disease relapsed in one renal transplant, raising the possibility of the presence of a transferable factor that could be part of the deposited fibrillar material or, alternatively, interfere with the glomerular handling of the deposited material.