Case report

Nephrotic syndrome after treatment with D-penicillamine in a patient with Wilson's disease

Sindrom nefrotic după tratament cu D-penicilamină la un pacient cu boala Wilson

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Abstract

Wilson's disease is an inherited autosomal recessive disorder of copper balance leading to accumulation of copper mainly in liver and brain result from absent or reduced function of copper-transporting P-type ATPase. Copper is an essential trace element but in Wilson's disease it accumulate to the point of toxicity. D-penicillamine is a classic drug for treatment of Wilson's disease. Its major effect is to promote the urinary copper excretion. The use of D-penicillamine in the therapy of Wilson's disease is known to be complicated by the development of various glomerular diseases. In this report we describe the development of nephrotic syndrome after 2 years treatment with D-penicillamine in a 31-year-old male undergoing treatment for Wilson's disease, with a prompt regression at the discontinuation of the drug. We present this case to draw attention to the rare complication as nephrotic syndrome in patients with Wilson's disease under D-penicillamine treatment and possible underlying causes. It is strongly necessary the therapy and clinical condition of patients with Wilson's disease to be monitoring regularly – we recommended monthly.

Key words: Wilson's disease; D-penicillamine; Urinary copper excretion

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Wilson's disease (WD) or hepatolenticular degeneration is an inherited autosomal recessive disorder of copper balance leading to accumulation of copper mainly in liver and brain as a result of absent or reduced function of copper-transporting P-type ATPase. ATP7B gene mutations causes decrease hepatocellular excre-tion of copper into bile. More than 500 mutations are known (1). Copper is an essential trace element, which is used as a cofactor by many enzymes playing vital roles but in WD it is accumulated to the point of toxicity (2). Clinical manifestation of WD is due to copper overload of copper in liver, brain, cornea, kidneys, and in

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other organs and tissues. Less common presentations of the disease include renal abnormalities such as aminoaciduria and nephrolitisis, hypercalciuria and nephrocalcinosis (1). Renal symptoms occur only in 1% of patients (4) usually as renal insufficiency with fulminant hepatic failure and hemolysis. WD is fatal if untreated (1, 2, 5). D-Penicillamine (D-PA) is a classic drug for treatment of WD and has been used frequently as first line therapy (6). The drug is a reductive chelator of metals and breakdown product of penicillin but is actually cysteine, doubly substituted with methyl groups. A free sulphydryl group acts as the copper-chelator (7). In 1956 penicillamine was introduced as the first oral drug for treating of WD by John Walshe (3, 8). Chelating drugs are used in cases where rapid reduction of high toxic copper levels is essential (9). The major effect of D-PA is to mobilize copper from liver and other organs and to promote urinary copper excretion (UCE) (1). D-PA also detoxifies tissue copper by promoting the synthesis of metallothionein, which forms a non-toxic complex with copper (10). The maintenance dose is usually 750–1500 mg/day administered in two or three divided doses (1). Anti-copper treatment in WD should be selected carefully because D-PA has serious toxicity (11). The drug may have a nephrotoxic action in WD, although this effect has mainly been described in other disorders such as rheumatoid arthritis (3). According to Grasedyck (12), the total incidence of side effects in D-PA treatment amounts to 30-60%, but newest data established possible adverse effects in 10-25% of the patients (7, 11, 13, 14). Therefore clear indications and regular evaluation of D-PA therapy are necessary. Because of D-PA side-effects profile in 20-30% of patients, discontinuation of therapy is necessary (1, 15, 16). Detailed data on long-term effectiveness of various drug therapies in WD are of lack (17) and there are few data of large cohorts (18). Weiss et al. (18) reported data of a study on 380 patients with Wilson disease from tertiary care centers in Germany and Austria, and 25 additional patients of EU-ROWILSON registry. Chelator treatment was assessed for the effect on neurologic and hepatic symptoms and for adverse effects leading to discontinuation of therapy. Adverse events leading to discontinuation of treatment were more frequent among those patients receiving D-PA than trientine (P =0.039) (18). In comparison with zinc salts, either alone or in combination with the D-PA, total discontinuations due to treatment failure or adverse events were more frequent in patients receiving D-PA (45%) or combination (36%) therapy then in patients receiving zinc (12%) (p=0.001 and p=0.02, respectively) (5). More common adverse effects on D-PA versus zinc sulfate (15% vs. 3%) reported Członkowska et al. (19). Side effects of D-PA can occur both early and late during the treatment period (10). Early side effects, 1 to 3 weeks after the beginning of the treatment, are sensitivity reactions with fever, rash, neutropenia, lymphadenopathy, thrombocytopenia and proteinuria (1, 10, 20). Delayed side effects occur in about 5% of cases, and can be caused by immunological factors, interference with collagen and elastin synthesis, or idiopathic factors (10). More serious side effects including Goodpasture's syndrome, Systemic lupus erythematosus (SLE), nephrotic syndrome, require immediate cessation of D-PA therapy (9, 13). Nephrotoxicity of D-PA is usually presented with proteinuria which may progress to nephrotic syndrome. Nephrotic syndrome is a late complication of D-PA treatment (1, 6). The first data for D-PA induced nephrotic syndrome was reported by Felleres and Shahidi in 1959 (21). D-PA induced proteinuria occurs in less than 10% of the patients with WD and usually begins over 1 year of treatment (22). Renal impairment caused by drugs can affect all structures of the kidney: glomeruli, tubules, interstitium and vessels. Pathogenetically mechanisms could involve toxicity, immune and circulatory

mechanisms. The most common injury of the kidney depends on the dose of the drug, the duration of drug administration or by immune mechanisms. Renal diseases caused by drugs are generally reversible, if the application of injurious medicament stop. In some cases, however, even cessation of the drug may not prevent the development of chronic renal failure. The mechanism of D-PA-induced renal disease is not well known. There are different explanations – D-PA affects glomerular basement membrane directly, possibly by interfering with cross-link formation (8); hypersensitivity mechanism (23); D-PA is a potent hapten and thereby enhances immunological presentation of glomerular basement or renal tubuloepithelial antigens (6). Proteinuria does not seem to be the only consequence of glomerular damage. It also may possibly cause tubular damage and initiate intestinal fibrosis and thus contribute to the progression of chronic renal diseases (24). Glomerular diseases can ensure during the course of WD and membranous nephropathy is the eventual pathology in the majority of these cases (25). Severe adverse effects of D-PA are autoimmune phenomena such as pemphigus, D-PA-induced lupus erythematosus, polymyositis/dermatomyositis, membranous glomerulopathy, hypersensitivity pneumonitis (like Good-pasture's syndrome) and myasthenia (all less than 1%) (9). Koraishy FM et al. first reported a case of cystic kidney disease likely associated with long-term D-PA therapy in a patient with cystinuria (26). In retrospective study in 42 Wilson's disease patients with mild liver disease diagnosed in childhood, between 1984 and 2012, Ranucci et al. (5) reported for 3 cases of proteinuria under D-PA therapy. Chang et al. (11) reported data on 65 patients with WD treated with a combination of D-PA and zinc sulfate with D-PA discontinuation due to adverse effects that occurred within the first 12 months of treatment in 10.5%. One of the studied patient developed nephrotoxicity.

In February 2013, a 31-year-old male was referred to Nephrology Department, University Hospital St. Ivan Rilski, Sofia, because of diagnosed nephrotic syndrome. Since January 2011, he was treated with D-PA because diagnosis of WD. D-PA was initiated at a dose 1500 mg/day and month later drug course was established as dose of 1000mg/day, administrated 4 times orally. According to the patient opinion, the therapy was regular and well tolerated. In 2013, typical nephrotic syndrome appeared with edema, proteinuria - 4.62g/L, hypoalbuminemia -14.75 g/L, hypercholesterolemia -11.29 mmol/L and microscopic hematuria. The patient had normal blood pressure. Impaired renal function was established on the base of testing of serum creatinine - 186 µmol/L and serum urea – 14.75 mmol/L. Patient's laboratory results at the moment of hospitalization are shown in *Table I*. Two months before hospitalization, normal urinary protein excretion was observed – 0.52 g/daily, so duration of proteinuria could be suggested to start at about 4-6 weeks before development of nephrotic syndrome. When renal disorder was established, D-PA therapy was stopped immediately and therapy with methylprednisolone 1000 mg/d, intravenously administrated, was applied for 5 days with a good effect. Patient's clinical status was improved and protein balance and renal function were restored: proteinuria – 1.5 g/24h, serum creatinine – 111 µmol/L, serum albumin – 25 g/L, serum cholesterol – 7.6 mmol/L. The patient was discharged after 15 days hospitalization with the following prescribed therapy: Dehydrocortizon (120 mg every other day) for a month with gradual reduction of the dose regimen up to 2 tablets (10 mg) for 14 days. In April 2013, two months later, the patient was hospitalized again for monitoring of his clinical status and treatment. He did not report any symptoms, associated with adverse drug effects. Proteinuria wasn't observed - 0.26g/L.

**Table I. Patient's laboratory results at the moment of hospitalization –
results outside the reference interval are marked with arrows**

Laboratory test	Patient's results	Reference value
White blood cells 10^9/L	6.70	3.5-10.5
Red blood cells 10^12/L	5.25	4.4-6.1
Hemoglobin g/L	170	135-180
Platelets 10^9/L	223	130-360
Glucose (mmol/L)	4.62	3.5-6.7
Aspartate aminostransferase (U/L)	↑ 687.5	<35
Alanine aminotransferase (U/L)	↑ 76	<40
Gamma-glutamyltransferase (U/L)	28	<55
Alkaline phosphatase (U/L)	57	<280
Creatine kinase (U/L)	58	21-195
Bilirubin, total (μmol/L)	6.24	3.4-21.0
Bilirubin, direct (μmol/L)	1.16	0.8-8.5
Creatinine (μmol/L)	↑ 186.43	44-134
Urea (mmol/L)	↑ 14.72	1.7 – 8.2
Total protein (g/L)	↓39.77	64 – 83
Serum albumin (g/L)	↓ 14.75	35 – 55
Total cholesterol (mmol/L)	↑ 11.29	<5.2
Triglycerides (mmol/L)	1.5	<2
C- reactive protein (mg/L)	2.53	<6
Erytrocyte sedimentation rate	↑ 64	<12
Sodium (mmol/L)	134.3	135-147
Potassium (mmol/L)	4.38	3.7-5.5
Chlorides (mmol/L)	109.0	93-112
Ceruloplasmine g/L	↓ 0.16	>2.0
Serum copper (μmol/L)	↓ 11.3	12.30-22.40
Total urine protein (g/L)	↑ 4.62	<1.5
IgA (g/L)	2.36	0.71-3.60
IgG (g/L)	8.04	6.58-18.37
IgM (g/L)	0.87	0.40-2.63
Rheumatoid factor	negative	negative
IgG autoantibodies against mutated citrullinated vimentin (Anti-MCV antibodies)	15.2	<20 /negative/
Anti-nuclear antibodies (ANAs) titer	1:20	< 1:80
Anti-mitochondrial antibodies (AMAs) titer	negative	<1:20 /negative/
Anti-smooth muscles antibodies (ASMAs) titer	1:40	<1:40
Anti-neutrophil cytoplasmatic antibodies (ANCAs) titer	negative	<1:20

The patient had taken out a detailed medical history and clinical examination. Routine clinical laboratory tests (serum glucose, creatinine, urea, total protein, albumin, total cholesterol, triglycerides, C-reactive protein, total and direct bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, creatine kinase, gamma-glutamyltransferase and uric acid) were run on a Roche automated clinical chemistry analyzer Cobas Integra 400 Plus, with original commercial reagents Roche, Germany, according to the recommended methods. Electrolytes (potassium, sodium and chlorides) were measured by ion-selective electrode using Medica EasyElectrolytes analyzer, USA. Ceruloplasmin and proteinuria were evaluated by automated clinical chemistry analyzer Cobas Integra 400 Plus, with original commercial reagents Roche, Germany. A complete blood count was done by Sysmex KX21N hematological analyzer. Urine reagent strips CYBOW, South Korea, were used for urinalysis. Many immunological tests were done: rheumatoid factor (RF) examined by Humatex RF, agglutination test, Human GmbH-65205 Wiesbaden, Germany; immunoglobulin subclasses (IgA, IgM, IgG) tested by nephelometry using (MininephTM Human analyzer and original reagents by The Binding Site Group LTD, UK); IgG autoantibodies against mutated citrollinatedvimentin (anti-MCV antibodies) were quantitatively measured by enzyme-linked immunosorbent assay (ELISA) using Anti-MCV ELISA, OrgentecDiagnostikaGmBh, Mainz, Germany. Antibodies against nuclear antigens were qualitatively evaluated by immunoblotting analytical technique, EUROIMMUN MedizinischeLabordiagnostika AG, LÜbeck, Germany: anti-nuclear ribonucleoprotein (anti-nRNP) antibodies, anti-Smith (anti-Sm) antibodies, anti-Ro (SS-A) antibodies, anti-La (SS-B) antibodies, anti-topoisomerase I (anti- Scl-70) antibodies, polymyositis-scleroderma antigen antibodies (PM-Scl), antibodies against cytoplasmic protein histidylt RNAsythetase (anti-Jo-1), anti-centromere B (anti-Cent.-B) antibodies, anti proliferative cell nuclear antigen (PCNA) antibodies, anti- dublestranded DNA (anti-dsDNA) antibodies, anti-nucleosomes antibodies, anti-Histone antibodies, anti-ribosomal P proteins (anti-Rib-P) antibodies, anti-mitochondrial M2 antibodies (AMA-M2). It is also examined anti-neutrophil cytoplasmic antibodies (ANCAs) by ANCA Substrate Slides, INOVA Diagnostics, Inc. San Diego, CA, USA. Anti-smooth muscles antibodies (ASMAs), anti- mitochondrial antibodies (AMAs) and ANAs titer were tested by Autoantibodies RL/RK/RS; OrgentecDiagnsotika GmbH, Mainz, Germany. Copper concentration in serum and urine was determined with flame atomic absorption spectrophotometry (Analyst 400, Perkin Elmer). Tests for viral hepatitis were done. For hepatitis C virus (HCV), ELISA kit Dia.Pro Italy, was used; measurement of HCV antibodies (HCV Ab) was done by combination between enzyme immunoassay method and a final fluorescent detection (ELFA) on Mini-Vidas, Biomérieux, France; markers for hepatitis B virus (HBV) infection and for hepatitis A virus (HAV) infection were measured, respectively – surface antigen of the HBV (HbsAg) and anti HAV-antibodies IgG and IgM (anti-HAV IgG and anti-HAV IgM). Microbiology urine analysis and pulmonary X-ray were also done. Test for HIV infectious was done by ELISA HIV Ab&Ag kit, Dia.Pro, Italy. Renal ultrasonography and percutaneous renal biopsy were performed. All laboratory analysis and diagnostic procedures were performed at University Hospital St. Ivan Rilski, Sofia.

Clinical examination found swelling of the face and ankles, weakened to absent vesicular breathing, no palpable liver and spleen. No data for fever, vomiting, jaundice or abdominal pain were observed. The patient had normal blood pressure. Succusio renalis test was negative. Clinical laboratory analyses presented the fol-

lowing results: Hematology tests showed normal erythrocyte, leukocyte and thrombocyte counts. Results of immunological tests fallen into the reference ranges: negative RF and anti-MCV antibodies– 15.2 U/ml (normal <20 U/ml), all investigated anti-nuclear antibodies (ANAs), AMAs, ASMAs and ANCAs were negative. Blood glucose 4.62 mmol/L was within the reference range (3.5-6.7 mmol/L), C-reactive protein (CRP) 2.53 mg/L was within the reference range (normal <6 mg/L). Aspartat-aminotranspherase (AST) and alanine-aminotranspherase (ALT) were increased – AST 687.5 U/L and ALT 76 U/L, as for AST the elevation was about 20 times and for ALT about 2 times above normal ranges. Serum creatinine (CREA) and urea were elevated, respectively 186.43 µmol/L and 14.72 mmol/L. Hypoproteinemia and hypoalbuminemia were established – total protein (TP) – 39.77 g/L (reference interval 64-83 g/L) and albumin (Alb) – 14.75 g/L (reference interval 35-55 g/L). High cholesterol levels were measured – 11. 29mmol/L (normal<5.2 mmol/). Severe proteinuria was observed – 4.62 g/24h (reference limits<1.5g/24h). Low levels of ceruloplasmin– 0.16 g/L (normal>2.0g/L) and serum copper – 11.3 µmol/L (reference interval 12.3-22.4 µmol/L) were established. Slightly increased cupriuresis was measured 48 hours followed off-treatment – 0.7 µmol/L (expected values <0.5 µmol/L). Microscopic hematuria was established. Markers for viral hepatitis and HIV infectious were negative. Microbiology urine analysis showed non-significant bacteriuria.

Pulmonary X-ray study showed presence of a small amount of liquid in dexter costodiaphragmatic sinus.

Renal ultrasonography showed normal kidney size and thickness of the parenchyma.
Renal biopsy revealed focal proliferative glomerulonephritis with discrete sclerosis, most likely as a substrate of idiopathic nephrotic syndrome. Puncture material contained 33 glomeruli; two of them were completely sclerotic. In the remaining glomeruli, was observed sparsely mesangial cell proliferation. In the minority of the glomeruli established discrete segmental sclerosis was observed. Examination depicted degenerative changes in the epithelial cells of the tubular apparatus. Protein cylinders were observed. Interstitium, and examined vessels were with a normal histological structure. Immunoflourescence measurement established mesangial and subepithelial 3-4+ IgM depositions.

Nephrotic syndrome was suspected on the base of existing body edema, a history of fatigue, proteinuria >3g/24h (4.62 g/24h), hypoalbuminemia <35 g/L (Alb - 14.75 g/L) and hypercholesterolemia >5.2 mmol/L (total cholesterol - 11.29 mmol/L). Impaired renal function was established – serum CREA and urea were elevated, respectively – 186.43µmol/L and 14.72 mmol/L. Active inflammatory process was rejected according to normal CRP and leucocytes count and absence of fever. HIV infection was excluded according to negative test for HIV antibodies. Viral hepatitis was also excluded according to negative markers for HCV, HBV and HAV infections. Blood glucose was with the normal range, so diabetes mellitus was excluded as well as diabetic nephropathy. According to negative immunological tests was excluded SLE, Sjögren's syndrome, polymiositis, autoimmune hepatitis, drug induced lupus and vasculitis. No amyloid depositions in the kidneys were found, according to renal biopsy, so diagnosis of amyloidosis was rejected. Microbiological examination of urine rejected eventual urinary infection. One possible reason for nephrotic syndrome could be trace element toxicity. But the patient had no history of eventual exposure to certain metals, so such hypothesis is rejected.

Our observation suggest prolonged D-PA treatment (during 2 years) as causative factor for proteinuria and nephrotic syndrome development, because other possible reasons were

excluded (systemic connective tissue diseases, amyloidosis, inflamation, viral or bacterial infections, trace elements toxicity and diabetes mellitus). Moreover, discontinuance of D-PA administration led to improved clinical status of the patient – swelling resolved, complaints of fatigue vanished, and laboratory tests for renal function reached back normal values.

Sözeri et al. reported that in patients with WD, the amount of all protein excreted in urine was significantly increased compared to controls (3). They considered increased excretion of tubular proteins in WD mainly during the first 2 years in D-PA treatment thus suggesting a close relationship to the primary metabolic disorder rather than to the drug effect. During this period, the tubular lesions due to copper depositions are regressed. Altered protein excretion in patients with WD on D-PA therapy depended on the treatment duration. D-PA treatment in the present case was prolonged for 24 months with mean dose 1000mg D-PA. Duration of the proteinuria was about 4–6 weeks with peak values of 5.0 g/24h. Once the diagnosis of WD is established, the treatment is for life and anti-copper treatment should be selected carefully because of toxicities of D-PA. The manner of disease manifestation, stage of the treatment, severity of the disease, potential side effects of the drug, efficacy of treatment and patient compliance should be considered (5, 27). Compliance with therapy is extremely important (13, 28). Strict control of the function of bone marrow, liver, and kidneys during the treatment is recommended. Monitoring of D-PA therapy includes two directions: the first is to assess eventual toxicity and the second is to evaluate the efficacy. For toxicity, it is necessary to follow-up complete blood cells count, serum CREA, serum urea, and urinalyses every 2 weeks for 4 to 6 months, later – monthly. Renal and liver functions should be evaluated every 3 months initially and then every 6 months (29). For efficacy, it is necessary to monitor 24-hour UCE and non-ceruloplasmin serum copper every 1, 3, 6, 12 months, then annually. Urine copper excretion 3-8 µmol (200-500 µg) per day while on treatment (1) and <0.5 µmol per day while off – treatment (30) are considered as criteria for adequate therapy.

In the present case, nephrotic syndrome was resolved and the treatment was continued with lower dose of D-PA – 500 mg/day with simultaneous administration of corticosteroids. It is strongly necessary, the therapy and clinical status of patients with WD to be monitored regularly. On the base of our experience, we recommend monthly monitoring of copper status, complete blood count and urine protein excretion.

Abbreviations

WD – Wilson's disease
D-PA – D-penicillamine
UCE – urinary copper excretion
SLE – systemic lupus erythematosus
RF – rheumatoid factor
IgA – immunoglobulin A
IgG – immunoglobulin G
IgM – immunoglobulin M
Anti-MCV-antibodies – auto-antibodies against mutated citrollinatedvimentin
ELISA – enzyme-linked immunosorbent assay
anti-nRNP – anti-nuclear ribonucleoprotein antibodies
anti-Sm – anti-Smith antibodies
anti-Ro (SS-A) – anti-SSA antibodies
anti-La (SS-B) – anti-SSB antibodies
anti-Scl-70 – anti-topoisomerase I antibodies
PM-Scl –anti polymiositis-scleroderma antibodies
anti-Jo-1 – antibodies to the cytoplasmatic protein histidyltRNAsythetase
anti-Cent.-B – anti-centromere B antibodies
PCNA – anti-proliferative cell nuclear antigen antibodies
anti-dsDNA – anti-dublestranded DNA antibodies

anti-Rib-P – anti-ribosomal P proteins antibodies
AMA-M2 – anti-mitochondrial antibodies M2
ANCAs – anti-neutrophil cytoplasmic antibodies
ASMAs – anti-smooth muscles antibodies
AMAs – anti-mitochondrial antibodies
HCV – hepatitis C virus
HCV Ab – hepatitis C virus antibodies
HAV – hepatitis A virus
HBsAg – surface antigen of the hepatitis B virus
anti-HAVIgG – anti hepatitis A virus immuno-globulin G
anti-HAVIgM - anti hepatitis A virus immuno-globulin M
HIV – human immunodeficiency virus
CRP – C-reactive protein
AST – aspartat-aminotranspherase
ALT – alanine-aminotranspherase
CREA – creatinine
TP – total protein
Alb – albumin

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