Case Report

J Ped. Nephrology 2016;4(2):70-73
http://journals.sbmu.ac.ir/jpn
DOI:

Nephrotic Syndrome after Treatment with D-Penicillamine in a Patient with Wilson's Disease- A Case Report

How to Cite This Article: Begum A, Rahman A, Akter M, Akter M, Islam A, Muinuddin G. Nephrotic Syndrome after Treatment with D-Penicillamine in a Patient with Wilson's Disease- A Case Report. J Ped Nephrology2016;4(2):70-73.

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Received: Mar-2016
Revised: Mar-2016
Accepted: Apr-2016

We report a case with Wilson's disease who developed nephrotic syndrome one year after starting D-pencillamine. After stopping D-penicillamine, only zinc was given for maintenance. His proteinuria resolved after four weeks of full dose prednisolone administration and three intravenous methylprednosolone injections for nephrotic syndrome. Membranous glomerulopathy is most commonly associated with nephrotic syndrome secondary to D penicillamine but isolated cases of minimal change lesions are also reported like our case.
The most likely cause of nephrotic syndrome in this child was the late complications of D-penicillamine. It also reemphasizes the importance of early monitoring for proteinuria and the need to shift to an alternative agent if side effects develop.

Keywords: Nephrotic syndrome; D-pencillamine; Wilson's disease.

Running Title: Nephrotic Syndrome after Treatment with D-Penicillamine

Introduction

Nephrotic syndrome (NS) is a common childhood kidney disease characterized by massive proteinuria (>40mg/m^2/hour), hypoalbuminemia (<2.5g/dl), generalized edema, and hypercholesterolemia (>200mg/dl) [1]. Nephrotic syndrome is primarily classified as primary NS that is not associated with systemic diseases, which accounts for 90% of childhood cases, and secondary NS that occurs as part of a systemic disease or is related to a drug or other toxins [2]. Quite a large number of drugs can cause NS like captopril, penicillamine, gold, NSAIDs, pamidronate, interferon, mercury, heroin, and lithium [3]. D-pencillamine and zinc are first line therapies for Wilson's disease.
D-pencillamine is a sulfhydryl chelating agent used as the primary therapy for Wilson's disease.

Proteinuria (nephrotic range), occurs in less than 10% of the patients with Wilson's disease and usually begins after more than 1 year of treatment with D-penicillamine [4]. As many as one-third of patients with significant proteinuria (>1-2 gm/24 hour) develop nephrotic syndrome if treatment continues [5,6].

Wilson's disease is an autosomal recessive disorder of hepatobiliary copper metabolism with symptoms related to hepatic and neurological copper toxicosis. Treatment is mandatory and, initial therapy consists of a chelating agent for most symptomatic patients. Because of its therapeutic efficacy, low cost, and safe clinical experience, D-penicillamine has been used frequently as first line therapy for Wilson's disease. However, significant side effects can occur, including nephrotoxicity that usually presents with proteinuria and, in severe cases, nephrotic syndrome. Membranous glomerulopathy is most commonly associated with nephrotic syndrome, but isolated cases of minimal change lesions have also been reported [7].

We report the late development of nephrotic syndrome in a 9 and a half year old boy with Wilson's disease 12 months after D-penicillamine treatment.

Case Report

A 9 and a half year old boy, the 1st issue of non consanguineous parents, who was a known case of Wilson's disease for 1 year and was on treatment with penicillamine, zinc, and pyridoxine presented with the complaints of a high grade intermittent fever for 6 days, swelling of the whole body and cola colored urine for 5 days, and loin pain for the last 2 days. The swelling first appeared in the periorbital region and then became generalized. He had no recent history of sore throat or skin infection, headache, vomiting, convulsion, unconsciousness, jaundice, hematemesis, melena, or contact with a tuberculosis patient. There was no family history of any liver disease.

On examination, the boy was ill looking, puffy, mildly pale, anicteric, edematous, and febrile. The vital signs were within the normal limit, and bed side urine albumin was 3+. Regarding anthropometry, his weight was 18 kg and his height was 118 cm. Height and weight were both below the 3rd centile for his age. Abdominal examination revealed ascitis and hepatosplenomegaly (Fig. 1). Renal angles were tender. Other systemic examinations were unremarkable

His urinalysis showed 3+ proteinuria, plenty of red blood cells, and 0-2 pus cells. Spot urinary protein to creatinine ratio was 6.5. The hematological picture showed mild anemia (Hb-10.9 gm/dl) and leucocytosis (TC-12,000/cmm), and the peripheral blood film showed mild normocytic normochomic anemia with leukocytosis. ESR was elevated (80mm in the 1st hr), the serum albumin level was 1.3 gm/dl and serum cholesterol was 282 mg/dl. Twenty-four hour total urinary protein was 3.5gm/day. The complement level was normal (C3 -1.44 gm/L , C4 -0.34 gm/L), and ANA and anti dsDNA titers were negative. Renal and liver functions were mildly impaired (serum creatinine 1 mg/dl & S. ALT: 88U/L, S. AST: 167U/L) and urinary copper was 213 mcgm/24 hours. Percutaneous renal biopsy was done which was consistent with minimal change disease. Immunofluroesence showed fine granular deposits with IgG (++), IgM (+), IgA (++) in the mesangium. Electron microscopy was not done due to unavailability.

Prednisolone was started at a dose of 60 mg/m^2/day as a single morning dose for nephrotic syndrome, D-penicillamine was stopped and only zinc was used for maintenance therapy for Wilson's disease. He achieved complete remission after 1 month of starting steroids and three intravenous methylprednisolone (Fig. 2).

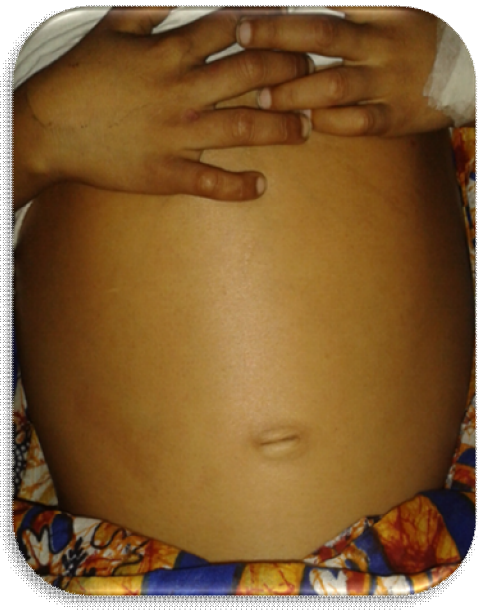

Figure 1. Ascites of the patient

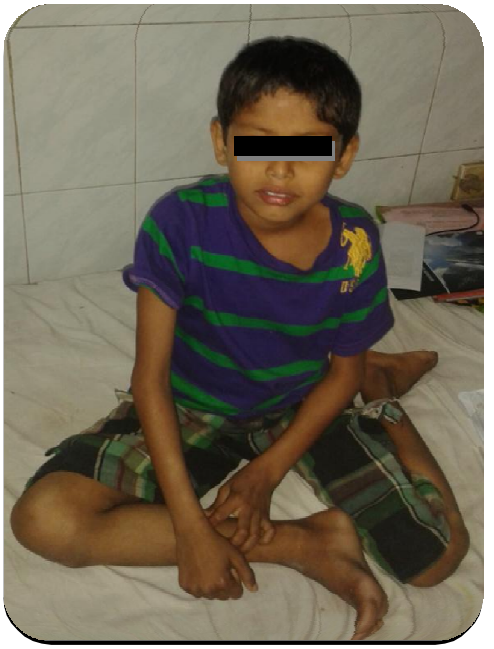

Figure 2. Photograph after remission

Discussion

Nephrotic syndrome is the most common type of glomerulonephritis in children of Asian subcontinent. It may be primary or secondary. Secondary nephrotic syndrome can occur either as a part of systemic disease or due to adverse reaction of drugs or toxins.

Wilson's disease is a rare autosomal recessive disorder of copper homeostasis with an incidence of 1/50,000 to 1/100000 births. It is progressive and potentially fatal if untreated; specific effective treatment is available [8].

Our patient, a 9 and a half year old boy and a known case of Wilson's disease, presented with swelling of the whole body and passage of red color urine after 1 year of penicillamine therapy. On the basis of proteinuria, hematuria, and histological findings consistent with minimal change disease, he was diagnosed with D-Penicillamine induced nephrotic syndrome. After diagnosis, penicillamine was stopped and he was treated with oral prednisolone with zinc and other supportive therapies. After 1 month of penicillamine discontinuation, he achieved complete remission.

D-Penicillamine (Dimethylcysteine) has been used successfully for many years in the treatment of Wilson's disease and cystinuria because of its chelating properties. It is also being used in the treatment of scleroderma and rheumatoid arthritis [9,10]. D-Penicillamine is a sulfur containing aminoacid that chelates copper and promotes its urinary excretion. Despite its effectiveness, D-Penicillamine presents significant adverse effects. Among them is proteinuria and nephrotic syndrome [11].

No serious allergic reactions have been reported following the use of D-pencillamine. Penicillin allergy is not a contraindication to the use of D-penicillamine [12]. In 20-30% of the patients with Wilson's disease, minor adverse effects of D-penicillamine are noted [4, 13]. During 1–3 weeks of therapy, patients can develop a hypersensitivity reaction. It has been supported that proteinuria can occur at any time, from six weeks to five years after D-penicillamine initiation, with a median time of seven months. The mean time from the first occurrence of proteinuria to nephrotic level proteinuria ranges from few weeks to several years. About 60%-70% of the patients with proteinuria may develop nephrotic syndrome if the treatment is continued. After stopping D-penicillamine, proteinuria may gradually decrease; however, 40% of the patients continue having proteinuria with no evidence of progressive renal disease [14]. Membranous glomerulopathy is the most common histological abnormality in 88% of the patients [4,7].

If the patients develop proteinuria or other side effects during treatment with D-penicillamine, a change in medication should be made to an alternative agent such as trientene. In our case, owing to the high cost of trientene, only zinc was used at the recommended dose for maintenance therapy.

The mechanism of D-penicillamine–induced renal disease is not known. In rheumatoid diseases, the drug may potentiate the glomerular damage from the existing rheumatoid immune complexes on specific regions of the glomerulus [7]. It may also act as a potent hapten, thus enhancing immunological presentation of glomerular basement or renal tubuloepithelial antigens, leading to Goodpasture's syndrome or membranous glomerulonephritis, respectively [4]. A strong correlation is indicated by the development of symptoms coincident with the introduction of D-penicillamine and complete resolution after the discontinuation of the drug.

Nephrotic syndrome due to minimal change disease has been previously described as a side effect of treatment with D-Penicillamine. The C3 levels are usually normal in children with nephrotic syndrome alone as in our case, but may

be low in children with hepatic synthetic dysfunction [15].

Wilson's disease itself may have tubular dysfunction but glomerulopathy is rare. Isolated minimal change disease can occur in a 10-year-old patient; yet, it is statistically more likely to occur in a much younger age group.

Conclusion

The most likely cause of nephrotic syndrome in this child was the late complication of D-penicillamine. It also re-emphasizes the importance of early monitoring for proteinuria and the need to shift to an alternative agent if side effects develop.

Conflict of Interest

None declared

Financial Support

None declared

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