Scientific Research Publishing

Open Journal of Nephrology, 2023, 13, 378-384
https://www.scirp.org/journal/ojneph
ISSN Online: 2164-2869
ISSN Print: 2164-2842

# Transient D-Penicillamine-Induced Nephrogenic Diabetes Insipidus during Treatment of a Patient with Cystinuria

## —D-Penicillamine-Induced Nephrogenic Diabetes Insipidus

**Kamel El-Reshaid[1*], Shaikha Al-Bader[2]**

[1]Department of Medicine, Faculty of Medicine, Kuwait University, Kuwait City, Kuwait
[2]Department of Medicine, Nephrology Unit, Amiri Hospital, Ministry of Health, Kuwait City, Kuwait
Email: *kamel@hsc.edu.kw

**How to cite this paper:** El-Reshaid, K. and Al-Bader, S. (2023) Transient D-Penicillamine-Induced Nephrogenic Diabetes Insipidus during Treatment of a Patient with Cystinuria. *Open Journal of Nephrology*, **13**, 378-384.
https://doi.org/10.4236/ojneph.2023.134035

**Received:** September 4, 2023
**Accepted:** November 20, 2023
**Published:** November 23, 2023



## Abstract

**Background:** Diabetes insipidus (DI) is a rare disorder characterized by inappropriate polyuria and hypo-osmolar urine. It is caused by inadequate production of antidiuretic hormone, in response to hypothalamic osmoreceptor-stimulation, from the pituitary gland (central DI) or resistance to its action at terminal distal convoluted tubules and collecting ducts (nephrogenic DI). Most cases of nephrogenic DI are caused by drugs, especially chronic lithium use. **The Case:** A 46-year-old man manifested such a disorder 8 months following d-Penicillamine (d-P) therapy for cystinuria. The drug was discontinued and the patient was managed conservatively with high fluid intake, diet low in protein and salt as well as alkalization of urine with Urolyte U to a pH > 7.5. Six weeks later, such side effect disappeared. Our patient had developed such phenomenon: a) without significant liver or renal disease to account for cumulative toxicity, and b) with a conventional dosage range of d-P. Such isolated toxicity indicates inherited a predisposition to this side effect. **Conclusion:** DI is a potential side effect of d-P therapy that is nephrogenic in site, transient in prognosis and an isolated phenomenon likely to reflect genetic predisposition.

## Keywords

Diabetes Insipidus, D-Penicillamine, Cystinuria, Genetic, Side Effect

## 1. Introduction

Diabetes insipidus (DI) is a rare disorder, affecting roughly 1 in 25,000 people or

about 0.004% of the global population [1]. It is defined by evidence of plasma hyperosmolality (greater than 300 mosm/l), urine hyperosmolality (less than 300 mosm/l or urine/plasma osmolality less than 1), polyuria (urinary volume greater than 4 mL/kg/hr to 5 mL/kg/hr) for two consecutive hours [2]. DI is caused by inadequate production of antidiuretic hormone (ADH), in response to hypothalamic osmoreceptor-stimulation, from the pituitary gland (central DI) or resistance to its action at terminal distal convoluted tubules and collecting ducts (nephrogenic DI). Idiopathic central DI accounts for 50% of cases and is usually associated with autoimmune lymphocytic hypophysitis [3]. However, it may follow: traumatic brain injuries, neurosurgery, meningioencephalitis, ischemia to pituitary and/or hypothalamus (Sheehan's syndrome), sarcoidosis, hemochromatosis, histiocytosis X, tumors and rarely genetic mutations in the ADH gene [4] [5]. On the contrary, most cases of nephrogenic DI are caused by drugs and rarely by hypercalcemia, hypokalemia, sickle cell disease, Sjogren's syndrome, polycystic kidney disease, pyelonephritis, post-obstructive polyuria, amyloidosis and rarely genetic mutations in the aquaporin-2 (AQP2) receptor genes for ADH [6]. Chronic lithium toxicity is the major cause of persistent nephrogenic DI in 10% of patients treated for >15 years [7]. Moreover, rare reports of nephrogenic DI may follow treatment with foscarnet, clozapine, demeclocyline, amphotericin B, orlistat, ifosfamide, ofloxacin, and vaptans [1]. For many years, d-Penicillamine (d-P) has been used to treat rheumatoid arthritis, Wilson's disease and cystinuria without significant renal disease except for a few cases of transient membranous nephropathy and rare ones with crescentic glomerulopathy [2]. Transient DI, induced by d-P has been reported once in a patient, with Wilson's disease, yet did not recur on re-challenge [8]. In this case presentation, we report the second case of DI induced by d-P and further define its characteristics.

## 2. The Case

A 46-year-old man presented with 6-week history of recurrent left loin pain for 1 month. He did not have significant past history of medical illness, surgery, allergy or chronic intake of medications. Family history was significant for cystine urolithiasis in 2 brothers. On his initial assessment, he was in pain which was better after antispasmodics. Blood pressure was 120/80 mm Hg and he was afebrile and with a body weight at 78 kg. Systemic examination did not show other abnormalities. Laboratory investigations showed normal peripheral leucocytic and platelet counts. Hemoglobin was normal. He had normal serum glucose, urea, creatinine, and electrolytes as well as liver and lipid tests. Urine routine and microscopy were normal except for excess RBCs/HPF. ECG and chest x-ray were normal. Abdominal and pelvic ultrasound (A&PUS) revealed left hydronephrosis with near-normal cortical thickness and echogenicity. Moreover, multiple small stones (<6 mm) were evident in both kidneys. CT scan of the abdomen and pelvis confirmed few <6 mm stones in the left ureter. Initially, he was treated with: a) antispasmodics to relive his colics, b) Tamsulosin 0.4 mg daily to

induce ureteral dilatation, and c) saline hydration with bicarbonates at a rate of 150 ml/hour with an attempt to achieve >2 liters of urinary output daily of alkaline urine at pH > 7.5. By the next 2 days, his pain was better. Repeat A&PUS showed resolution of left hydronephrosis and fewer stones in both kidneys. Straining of the voided urine detected a few stones. Stone analysis, using infrared spectroscopy, revealed cystine stones. Moreover, 24-hour urine tests showed: a) normal levels of calcium, phosphorus, uric acid, magnesium, citrate and oxalates yet cystine levels were high at 449 umol (normal range 28-115 umol/L). Subsequently, the patient was discharged on the following treatment: a) high oral fluid intake (>2 liters/day), b) diet low in sodium and protein, and c) use of Urolyte U (potassium sodium hydrogen citrate) to achieve urine pH > 7.5, and d) d-penicillamine. On follow-up, the patient remained asymptomatic and A&PUS did not show urolithiasis. Moreover, his urine cystine decreased to 75 umol/L. Eight months later, he developed severe and inappropriate polyuria with frequent voiding of large amounts of urine, even nocturnal, that was associated with 7 kg weight loss within 2 months. Laboratory tests showed hypernatremia, urine hypo-osmolality at 280 mosm/l and urine/plasma at osmolality 0.7. Moreover, there was no change in urine osmolality after water deprivation test indicating DI. D-Penicillamine was suspected to be the culprit, for his DI, and hence was discontinued. Subsequent tests showed: a) failure of IV desmopressin to raise urine osmolality, b) lack of clinical improvement with a trial of Minirin melt 120 mg for 2 weeks, c) normal posterior pituitary bright-spot on MRI images, and d) high level of plasma copeptin at 24 pmol/L (normal range: 1 - 13.8) indicating nephrogenic DI. Following discontinuation of d-P, the patient was managed with high-intake of water. Within 6 weeks, urine output decreased and his weight loss improved as well as his biochemical derangements (**Table 1**). With regards to his cystinuria, he was managed only with high-fluid intake and alkalinization of urine. Six months later, he maintained normal urine output and A&PUS did not show urolithiasis.

## 3. Discussion

Cystinuria is an uncommon autosomal-recessive genetic disease that leads to frequent urolithiasis. It accounts for 1% of those presenting <30 years and 10% in children with variable ethnic population prevalence [9]. Type I heterozygote shows normal amino acid urinary pattern, whereas Types II and III are characterized by an increase of cystine, lysine, ornithine, and arginine urinary excretion [10]. A homozygous patient typically excretes >250 mg or cystine/g of creatinine in a 24-hour urine collection [11]. Early diagnosis and management, especially of homozygous type, is essential to avoid urinary cystine supersaturation and rapid progressive cystine stones. Moreover, such large and solid stones are extremely difficult to manage, at advanced stages, with conventional lithotripsy and usually require percutaneous nephrolithotomy or open surgery [12]. Our patient presented with typical features of homozygous cystinuria that indicated

Table 1. Demographic and biochemical changes in the patient with cystinuria after d-Penicillamine therapy.

| | Time with regards d-P therapy (months) | | | |
|---|---|---|---|---|
| | 0 | 8 | 9.5 | 14 |
| **Parameter:** | | | | |
| **A-Weight** (kg)**:** | 72 | **65** | 70 | 72 |
| **B-Urine output** (liters/day)**:** | 1.5 | **5** | 2 | 1.5 |
| **C-Blood pressure** (mm Hg)**:** | 120/80 | **90/60** | 120/80 | 120/80 |
| **D-Laboratory tests:** | | | | |
| 1) Hemoglobin: | 134 | **160** | 130 | 130 |
| 2) Serum sodium: | 138 | **152** | 138 | 138 |
| 3) Serum copeptin level: | ND | **24** | 11 | 9 |
| 4) Urine osmolality: | ND | **280** | 2100 | 2600 |
| 5) Urine/plasma osmolality: | ND | **0.7** | 1 | 1 |
| 6) 24-hour urine cystine: | 449 | **120** | 420 | 432 |
| **E-Urolithiasis by US:** | None | **None** | None | None |
| **Therapy:** | | | | |
| d-P 250 mg X3 | | | | |
| Minirin melt 120 mg | | | | |
| 24-hour oral fluid intake (liters): | 2-3 | **5-6** | 2-3 | 2-3 |
| Urine pH with alkali therapy | 7-8 | **7-8** | 7-8 | 7-8 |

Normal levels of: hemoglobin: 13 - 16 g/L, sodium: 135 - 150 mmol/L, copeptin: 1 - 13.8 pmol/L, urine osmolality: 50 - 1200 mOsm/kg, urine/serum osmolality: 1 - 3.

aggressive therapy. The latter included high water intake, diet low in sodium and protein, aggressive alkalinization of urine and d-P as a cystine-binding thiol drug (CBTD). Unfortunately, in our patient, a rare side effect, of nephrogenic DI, limited the use of d-P maintenance use. In 1956, Walshe first proposed the use of d-P, as a chelating agent for copper, in treatment of hepatolenticular degeneration (Wilson's disease) [13]. The d-isomer is the safest of its other isomers [14]. Since then, the drug has been used in treatment of multiple disorders viz. a chelator in lead and arsenic poisoning, a binder to cysteine yielding a more soluble disulfide in cystinuria, and, a disease modifying antirheumatic drug to decrease T-lymphocytes, IL-1 and collagen cross-linkage in refractory rheumatoid arthritis and scleroderma. Subsequently, the drug-use has been limited to Wilson's disease and cystinuria due to the introduction of more potent and safe chelators in poisoning and TNF-inhibitors for autoimmune diseases. Moreover, information about the drug's toxicity is evolving despite the rarity of its 2 indica-

tions. Several undesirable side effects of d-P have been encountered with nearly one third of patients suffer from: a) diarrhea, b) acute sensitivity reactions manifested by fever, pancytopenia, adenopathy, urticarial rash and bullous pemphigoid on prolonged administration of more than 2 gm/day, and c) systemic disorders viz. psychiatric disease, hepatotoxicity, arthritis, vasculitis, bronchiolitis obliterans, myasthenia and reversible optic neuritis [2]. Though renal failure was rarely encountered with the drug-use, transient nephrotic syndrome associated with membranous glomerulopathy was the main renal cause for discontinuation. As mentioned earlier, only 1 case report added self-limited and transient DI to its long list of side effects. Our case report confirms such association and further defines its nephrogenic site of insult since it was associated with lack of response to IV desmopressin and Minirin as well as intact bright spot in MRI of post pituitary and finally high plasma copeptin indicating adequate ADH-release [15] [16] [17]. Moreover, it should be noted that such phenomenon was: a) a toxic reaction since it was associated with gradual evolution (8 months) and slow recovery (6 weeks) and b) a transient one. The latter may have been similar to lithium toxicity affecting sodium channels in the collecting tubules via decrease of aquaporin-2 (AQP2) receptor expression and transcription [18]. Such toxicity leads to failure of the cascade of intracellular cascade of events, among which protein kinase A (PKA) activation and movement of transport vesicles containing the water channel (AQP2) from intracellular storage compartments to the apical surface of the principal cells [19]. Interestingly, and contrary to our multiple cystinuria patients treated for many years with d-P, our patient developed such phenomenon: a) without significant liver or renal disease to account for cumulative toxicity, and b) with conventional dose range of d-P. Such isolated toxicity indicates an inherited a predisposition to this side effect. At present, our patient is stable on conservative therapy without d-P for >6 months. Future treatment considerations, if cystinuria recurs, may include other cystine-binding thiol drug (CBTD) viz. Tiopronin or L-cystine dimethyl ester (L-CDME) and L-cystine methyl ester (L-CME) [20].

## 4. Conclusion

DI is a potential side effect of d-P therapy that is nephrogenic in site, transient in prognosis and an isolated phenomenon likely to reflect genetic predisposition.

## Statement of Ethics

The case was reported according to the World Medical Association Declaration of Helsinki. There was no new or investigational drug added to the patient's maintenance therapy and they were not subjected to any harmful or injurious investigation.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

## References


[1] Christ-Crain, M., Bichet, D.G., Fenske, W.K., Goldman, M.B., Rittig, S., *et al.* (2019) Diabetes Insipidus. *Nature Reviews Disease Primers*, **5**, Article No. 54. https://doi.org/10.1038/s41572-019-0103-2

[2] Mejias, S.G. and Ramphul, K. (2023) Penicillamine. StatPearls Publishing, St. Petersburg, FL. https://www.ncbi.nlm.nih.gov/books/NBK513316/

[3] Imura, H., Nakao, K., Shimatsu, A., Ogawa, Y., Sando, T., *et al.* (1993) Lymphocytic Infundibuloneurohypophysitis as a Cause of Central Diabetes Insipidus. *New England Journal of Medicine*, **329**, 683-689. https://doi.org/10.1056/NEJM199309023291002

[4] Robertson, G.L. (2001) Antidiuretic Hormone: Normal and Disordered Function. *Endocrinology and Metabolism Clinics of North America*, **30**, 671-694. https://doi.org/10.1016/S0889-8529(05)70207-3

[5] Schernthaner-Reiter, M.H., Stratakis, C.A. and Luger, A. (2017) Genetics of Diabetes Insipidus. *Endocrinology and Metabolism Clinics of North America*, **46**, 305-334. https://doi.org/10.1016/j.ecl.2017.01.002

[6] Sands, J.M. and Bichet, D.G. (2006) Nephrogenic Diabetes Insipidus. *Annals of Internal Medicine*, **144**, 186-194. https://doi.org/10.7326/0003-4819-144-3-200602070-00007

[7] Grünfeld, J.P. and Rossier, B.C. (2009) Lithium Nephrotoxicity Revisited. *Nature Review of Nephrology*, **5**, 270-276. https://doi.org/10.1038/nrneph.2009.43

[8] Lupescu, I.C., Iacob, S., Iacob, R., Anghel, D., *et al.* (n.d.) Diabetes Insipidus during D-Penicillamine Treatment of a Wilson Disease Patient. https://simul-europe.com/2019/cony/Files/383.pdf

[9] Eggermann, T., Venghaus, A. and Zerres, K. (2012) Cystinuria: An Inborn Cause of Urolithiasis. *Orphanet Journal of Rare Diseases*, **7**, Article No. 19. https://doi.org/10.1186/1750-1172-7-19

[10] Rosenberg, L.E., Downing, S., Durant, J.L. and Segal, S. (1966) Cystinuria: Biochemical Evidence for Three Genetically Distinct Diseases. *Journal of Clinical Investigations*, **45**, 365-371. https://doi.org/10.1172/JCI105351

[11] Milliner, D.S. (1990) Cystinuria. *Endocrinology and Metabolism Clinics of North America*, **19**, 889-907. https://doi.org/10.1016/S0889-8529(18)30299-8

[12] Azer, S.M. and Goldfarb, D.S. (2023) A Summary of Current Guidelines and Future Directions for Medical Management and Monitoring of Patients with Cystinuria. *Healthcare*, **11**, Article 674. https://doi.org/10.3390/healthcare11050674

[13] Walshe, J.M. (1956) Wilson's Disease: New Oral Therapy. *The Lancet*, **270**, 25-26. https://doi.org/10.1016/S0140-6736(56)91859-1

[14] Ariens, E.J. (1989) Chiral Separations by HPLC. Ellis Horwwod, Chichester, 31-68.

[15] Babey, M., Kopp, P. and Robertson, G.L. (2011) Familial Forms of Diabetes Insipidus: Clinical and Molecular Characteristics. *Nature Review in Endocrinology*, **7**, 701-714. https://doi.org/10.1038/nrendo.2011.100

[16] Kurokawa, H., Fujisawa, I., Nakano, Y., Kimura, H. and Akagi, K. (1998) Posterior Lobe of the Pituitary Gland: Correlation between Signal Intensity on T1-Weighted MR Images and Vasopressin Concentration. *Radiology*, **207**, 79-83. https://doi.org/10.1148/radiology.207.1.9530302

[17] Morgenthaler, N.G., Struck, J., Alonso, C. and Bergmann, A. (2006) Assay for the Measurement of Copeptin, a Stable Peptide Derived from the Precursor of Vaso-

pressin. *Clinical Chemistry*, **52**, 112-119. https://doi.org/10.1373/clinchem.2005.060038

[18] Davis, J., Desmond, M. and Berk, M. (2018) Lithium and Nephrotoxicity: Unravelling the Complex Pathophysiological Threads of the Lightest Metal. *Nephrology*, **23**, 897-903. https://doi.org/10.1111/nep.13263

[19] Boone, M. and Deen, P.M. (2008) Physiology and Pathophysiology of the Vasopressin-Regulated Renal Water Reabsorption. *Pflügers Archiv—European Journal of Physiology*, **456**, 1005-1024. https://doi.org/10.1007/s00424-008-0498-1

[20] Moussa, M., Papatsoris, A.G., Abou Chakra, M. and Moussa, Y. (2020) Update on Cystine Stones: Current and Future Concepts in Treatment. *Intractable Rare Disease Research*, **9**, 71-78. https://doi.org/10.5582/irdr.2020.03006