CEN Case Reports (2024) 13:93–97
https://doi.org/10.1007/s13730-023-00806-6

CASE REPORT

Distal renal tubular acidosis as presenting manifestation of Wilson disease in a 11-year-old girl

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Received: 28 February 2023 / Accepted: 27 June 2023 / Published online: 6 July 2023

Abstract

A 11-year-old girl was referred to the pediatric nephrology services of our hospital for evaluation of vitamin-D-refractory rickets. She was born to second-degree consanguineous parents. On examination, she had wrist widening and bilateral genu varum. She had normal anion gap metabolic acidosis, hypokalemia, and hyperchloremia. The fractional excretion of bicarbonate was 3% and the urine anion gap was positive. She also had hypercalciuria, but no phosphaturia, glucosuria or aminoaciduria. In view of a family history of an elder sister having rigidity with cognitive and speech impairment, an ophthalmic evaluation by slit lamp examination was performed in the index case that revealed bilateral Kayser–Fleischer rings. Serum ceruloplasmin was low and 24-h urine copper was elevated in the index case. Whole exome sequencing unveiled a novel pathogenic variant in *exon 2* of the *ATP7B* gene *(chr13: c.470del; Depth: 142x)* (homozygous) that resulted in a frameshift and premature truncation of the protein, 15 amino acids downstream to codon 157 *(p. Cys157LeufsTer15; NM_000053.4)* confirming Wilson disease. There were no mutations in the *ATP6V0A4*, *ATP6V1B1*, *SLC4A1, FOXI1*, *WDR72* genes or other genes that are known to cause distal RTA. Therapy with D-penicillamine and zinc supplements was initiated. A low dose of 2.5 mEq/kg/day of potassium citrate supplementation normalized the serum bicarbonate levels. This case was notable for the absence of hepatic or neurological involvement at admission. Wilson disease is well known to cause proximal renal tubular acidosis and Fanconi syndrome, with relatively lesser involvement of the distal renal tubules in the literature. However, isolated distal renal tubular involvement as presenting manifestation of Wilson disease (without hepatic or neurological involvement) is rare and can lead to diagnostic confusion.

Keywords Wilson disease · Rickets · Metabolic acidosis · Hypercalciuria · Distal RTA

Introduction

Wilson disease is an autosomal recessive disorder involving the ATP7B gene (chromosome 13q) expressed in liver, brain, kidneys, and some other organs which encodes for the copper transporting P-type ATPase [1]. When intracellular copper is in excess, ATP7B enhances its excretion into the bile by exocytosis. ATP7B mutations cause reduced copper-bound ceruloplasmin synthesis, impairing excretion of copper, and increased copper levels in the cytoplasm, nucleus, and mitochondria leading to cellular damage. Clinical manifestations depend on the site of copper deposition**.** Renal manifestations include renal stones and renal tubular acidosis (RTA) (including Fanconi syndrome) [2]. We herein report a case of Wilson disease with initial presentation of rickets and isolated renal involvement (in the form of distal RTA) without hepatic or neurological involvement.

Case report

A 11-year-old girl was referred to the pediatric nephrology clinic of our hospital with complaints of progressive bowing of the legs over the last 12 months. There was no history of fractures, bone pain, fever, weight loss, polydipsia, polyuria, muscle cramps, constipation, tetany or seizures. She was diagnosed as rickets and had been prescribed vitamin D supplements elsewhere for 4 months prior to presentation at our hospital, but there was no radiological healing line, for which she had been referred. Her

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scholastic performance was good, and she had received age-appropriate vaccines till date. She was second-born to second-degree consanguineous parents, with uneventful antenatal, perinatal, and neonatal history. The developmental milestones were normal for age. There was no history suggestive of rickets or bony deformities in the family. On probing further, the parents gave history of her 14-year-old elder sister who was bed-ridden with progressive rigidity, poor speech and cognition, and had poor intelligence according to the parents for the last 4 years.

On examination, the anthropometric measurements of the index case were within normal range with weight 37.5 kg (– 0.39z), height 132 cm (– 1.23z), and body mass index 21.5 (+ 0.32z). Her vital signs were stable with normal blood pressure readings (100/70 mm Hg). She had bilateral wrist widening and bilateral genu varum. The dentition was normal. There was no pallor, icterus, clubbing, or lymphadenopathy. There was no malar rash, alopecia, rash over any part of the body, arthritis, or oral ulcers. There was no hepatosplenomegaly, ascites or palpable renal or abdominal mass. The cardiac and respiratory system examinations were normal. The neurological examination was unremarkable.

The blood investigations at presentation revealed normal anion gap (8 mEq/L) metabolic acidosis, hypokalemia, and hyperchloremia (Table 1). The blood peripheral smear was normal, with no spherocytes or ovalocytes. The teeth were normal, with no abnormal pigmentation. The fractional excretion of bicarbonate was 3% (Table 1). Urine anion gap was positive (+ 4 mEq/L). She was found to have hypercalciuria, but no phosphaturia, glucosuria, or aminoaciduria. The skeletal radiographs were suggestive of metaphyseal widening, cupping, fraying of the long bones of the forearm, and fraying of the bilateral femoral metaphysis (non-healing rickets). Hearing evaluation by pure tone audiometry was negative. The ultrasonogram of the kidneys showed normal sized kidneys, normal echogenicity, and maintained corticomedullary differentiation without any evidence of nephrocalcinosis or cysts.

Since there were no features suggestive of secondary distal RTA (dRTA), primary dRTA, possibly due to

Table 1 Investigations in the patient at presentation

Parameter	Patient's value	Reference value
Hemoglobin (g/dL)	11.5	11.5–15.5
Total leukocyte count (cells/μL)	7600	4000–11000
Platelet count (cells/μL)	201000	150000–400000
Blood urea (mg/dL)	16	10–40
Serum creatinine (mg/dL)	0.48	0.5–0.9
Serum sodium (mEq/L)	135	135–145
Serum potassium (mEq/L)	2.9	3.5–5.5
Serum calcium (mg/dL)	10.2	9–11
Serum phosphate (mg/dL)	4.6	3.5–5.5
Serum magnesium (mg/dL)	2.0	1.7–2.7
Serum albumin (g/dL)	4.5	3.5–5
Serum uric acid (mg/dL)	4.3	2.7–5.9
Serum bicarbonate (mEq/L)	15	22–26
Serum pH	7.35	7.35–7.45
Serum chloride (mEq/L)	112	98–104
Serum alkaline phosphatase (IU/L)	634	93–309
Serum intact parathormone (pg/mL)	35	15–30
Urine pH	7.0	< 5.5
Spot urine calcium: creatinine ratio	0.8	< 0.2
24-h urine calcium (mg/kg/24 h)	5.1	< 4
Urine Benedict test for reducing substances	Negative	Nil
TmPGFR (mg/dL)	4.3	2.8–4.4
Urine amino acids	Negative	Nil
Urine protein: creatinine ratio	0.1	< 0.2
Urinalysis	No RBC/WBC in urine, no proteinuria by dipstick	–
Serum vitamin D (ng/mL)	28	> 20
Fractional excretion of bicarbonate	3%	< 5%
Urine anion gap	+ 4 mEq/L	–

mutations in *ATP6V0A4*, *ATP6V1B1*, or *SLC4A1 genes* was considered as the probable cause. However, Wilson disease was also considered because of the significant family history in the sibling who was having neurological problems. Subsequently, ophthalmic evaluation by slit lamp examination revealed bilateral Kayser–Fleischer rings. Further evaluation revealed that serum ceruloplasmin was reduced (11 mg/dL) and 24-h urine copper was elevated (110 mcg/24 h). However, her liver function tests were normal (total bilirubin 0.36 mg/dL, direct bilirubin 0.10 mg/dL, serum albumin 4.5 g/dL, aspartate aminotransferase 22 IU/L, alanine aminotransferase 23 IU/L, prothrombin time 12.3 s with INR1.08 and activated partial thromboplastin time 31.5 s). The Doppler ultrasonogram of hepatoportal axis was not suggestive of portal hypertension. Magnetic resonance imaging (MRI) of the brain was unremarkable. Whole exome sequencing of the index case unveiled a novel pathogenic variant—a homozygous single base pair deletion in *exon 2* of the *ATP7B* gene *(chr13: c.470del; Depth: 142x)*—that resulted in a frameshift and premature truncation of the protein, 15 amino acids downstream to codon 157 *(p. Cys157LeufsTer15; NM_000053.4)* confirming the diagnosis of Wilson disease. The variant has extremely low frequency in population databases (has not been reported in the 1000 genomes, and gnomAD). The in-silico prediction of the variant is damaging by MutationTaster2 and the reference region is conserved across species. The variant has been classified as Pathogenic as per American College of Medical Genetics and Genomics (ACMG) 2015 variant classification (PVS1, PM2). There were no mutations identified in the *ATP6V0A4*, *ATP6V1B1*, *SLC4A1, FOXI1*, *WDR72 genes* or other genes that are known to cause distal RTA. She was initiated on penicillamine and zinc therapy.

The child is doing well on potassium citrate supplements at a 1-year follow-up and her current serum bicarbonate is 22 mEq/L and serum potassium is 3.6 mEq/L. The bony deformities have not worsened. She has not developed any other manifestations of Wilson disease so far, including hepatic or neurological manifestations. The recent 24-h urine copper excretion on penicillamine treatment is within normal limits [40mcg/day].

The parents were counseled for the evaluation of the elder sibling, who was confirmed as Wilson disease by detection of bilateral Kayser–Fleischer rings, and elevated 24-h urine copper (210 mcg/24 h) with low serum ceruloplasmin (10 mg/dL). However, she did not show any manifestations of dRTA like rickets, polyuria, polydipsia, hypokalemia, etc. The child was evaluated for the same (pH-7.35, bicarbonate-22.6, serum sodium 135 mEq/L, potassium 4.2 mEq/L, chloride 102 mEq/L) and was found to be normal. She was also initiated on penicillamine and zinc therapy.

Discussion

Our patient was referred for the evaluation of vitamin-D-refractory rickets. The clinical constellation of normal anion gap metabolic acidosis, hypokalemia, and hyperchloremia led us to suspect RTA as the cause for refractory rickets. The presence of low fractional excretion of bicarbonate and positive urine anion gap with hypercalciuria; and absence of phosphaturia, glucosuria or aminoaciduria led us to suspect distal RTA. Although Wilson disease was considered a possibility because of the significant family history in the sibling, the absence of obvious clinical involvement of liver and brain posed a diagnostic challenge in this child. The presence of Kayser–Fleischer rings, reduced serum ceruloplasmin, and increased 24-h urine copper favored the diagnosis of Wilson disease which was later confirmed by genetic analysis. There were no mutations identified in the *ATP6V0A4*, *ATP6V1B1*, *SLC4A1, FOXI1* or *WDR72 genes* that are known to cause distal RTA. Predominant renal tubular/bony involvement in Wilson disease has been rarely described in literature in a few reports [2–7]. However, all these cases had clinical or biochemical involvement of liver.

The index case presented as dRTA, in the absence of typical features of Wilson disease (neurological or hepatic involvement), probably due to early deposition of copper in distal tubules resulting in inability to excrete H^+, which further led to softening of bones and bony deformities. Tubular injury in Wilson disease occurs with deposition of copper in the mitochondria (due to affinity for ATPase) in the proximal and distal convoluted tubular epithelium causing cell death which manifests as RTA. In children, distal RTA is usually primary and the most common mutations include the genes *ATP6V0A4*, *ATP6V1B1*, *SLC4A1, FOXI1*, and *WDR72*. The most common acquired causes of distal RTA include systemic lupus erythematosus, Sjogren syndrome, Wilson disease, chronic obstructive uropathy, and drugs (amphotericin, lithium) [8].

There are anecdotal reports of Wilson disease presenting with manifestations of dRTA. Palkar et al. reported 2 siblings presenting with rickets and pathological fractures secondary to distal RTA as the initial manifestation of Wilson disease. Further evaluation revealed hepatosplenomegaly but there was no neurological involvement [2]. Subrahmanyam et al. reported a 16-year-old male with lower limb weakness secondary to hypokalemia caused by distal RTA. This patient had both hepatomegaly and neurological involvement on examination [3]. Thapa et al. and Chakraborty et al. also reported a similar presentation of Wilson disease with recurrent lower limb weakness. These patients had hepatic involvement in the form of deranged liver function tests but no neurological involvement was

found [4, 5]. Kalra et al. reported 14-year-old female with bilateral renal calculi precipitated by distal RTA in Wilson disease and had deranged liver function tests [6]. Stefano et al. reported a case of Wilson disease presenting with polyuria and polydipsia secondary to distal RTA. He had transaminitis but no neurological involvement was noted [7]. All these patients had positive finding of Kayser–Fleischer rings on ophthalmological examination which led the authors to suspect Wilson disease. Our patient had isolated renal manifestation and Kayser–Fleischer rings without any hepatic or neurological involvement which is different from the previous reported cases.

A case series in patients with Wilson disease has previously described that more than half of patients with Wilson disease had RTA (16 out of 25). Majority had dRTA (7 out of 16), with a significant number having proximal RTA (4 out of 16) and mixed RTA (5 out of 16). RTA was more common in patients with prolonged hepatic illness, unlike our case [9].

Apart from dRTA, other mild forms of renal disturbances in Wilson disease are often missed. Additionally, in Wilson disease, increased urinary calcium excretion results from impaired reabsorption in tubules and excessive bone resorption, thereby causing nephrocalcinosis, nephrolithiasis and microscopic hematuria. Glomerular injury can also occur with deposition of copper causing proteinuria but this occurs more often due to D-penicillamine therapy [10]

Wilson disease has been described to have a spectrum of manifestations ranging from being diagnosed in pre-symptomatic phase in siblings of diagnosed Wilson disease or those with elevated transaminases, isolated Kayser–Fleischer ring in the absence of neurological manifestations, liver or mixed clinical manifestations [11]. Kayser–Fleischer rings are present in 100%, 50%, and 40% of patients presenting with neuropsychiatric, hepatic, and pre-symptomatic disease [12]. The variant reported in our case is novel. It is yet to be seen if findings similar to our case are reported in future case reports. It is also unclear if the index case is currently in the pre-symptomatic stage (for neurological and hepatic manifestations) and might progress to have neurological or hepatic manifestations in the future.

It is interesting to note such wide phenotypic difference in the same family. The phenotype in Wilson disease is so varied that even in siblings, the presentation may not be the same. Despite high intra-familial concordance of biochemical and clinical presentation in Wilson disease, a small percentage shows varied phenotypic presentation [13]. Walshe et al. reported two siblings with isolated organ involvement, one with neurological and the other with hepatic dysfunction [14]. Sapuppo et al. reported two sisters with same genotype having different phenotype of isolated neurological and hepatic involvement. It is hypothesized that this phenotypic variability might be because of intervention of other copper metabolism regulatory modifying genes [15].

Treatment in Wilson disease involves managing both the cause and the effect of the disease. D-penicillamine is the preferred therapy for Wilson disease. Trientine and ammonium tetrathiomolybdate are the other chelating agents available in case of D-penicillamine toxicity or intolerance. The role of these drugs, however, in reversing the Wilson disease-induced dRTA is unlikely and the tubular involvement warrants alkali supplements [16]

Alkali supplements are advised to patients with distal RTA, titrated to target adequate serum bicarbonate levels (target value 22 mEq/L). Potassium-citrate is the alkali supplement of choice. Sodium containing supplements are not preferred because of two reasons: (i) sodium increases the amount of extracellular fluid, decreases bicarbonate reabsorption and therefore, enhances the need for alkali; (ii) it increases calcium excretion in the urine and may cause nephrocalcinosis. The amount of alkali required is highest in infancy and decreases with age. Early and adequate alkali supplementation optimizes growth velocity, corrects rickets, reduces hypercalciuria by increasing urinary citrate excretion, and thus reduces the incidence of nephrocalcinosis. Reduction of sodium intake in the diet and increased intake of fluids and citrus fruits are advised. Urine examination for hypercalciuria and ultrasonography of the kidneys are important tools for monitoring for nephrocalcinosis [17]. This child was started on D-penicillamine 20 mg/kg/day along with zinc supplementation. A low dose of 2.5 mEq/kg/day of potassium citrate supplementation normalized the serum bicarbonate levels in our patient, which is typically noted in distal RTA.

This case illustrates a rare presentation of Wilson disease with distal RTA and refractory rickets without hepatic or neurological manifestations. Though proximal RTA and Fanconi syndrome are classically observed in Wilson disease, this disease can also present with distal RTA rarely. Pediatric nephrologists should be aware that distal RTA causing rickets can be a rare presenting manifestation of Wilson's disease.

Although all isolated cases of distal RTA without hepatic and neurological manifestations may not merit testing for Wilson disease, it is worth noting that in the setting of late presentation of dRTA and a positive family history, it was prudent to evaluate for Wilson disease as primary cause in index case. A routine evaluation of ophthalmological and hearing assessment as a part of tubular diseases is more important, and will provide clues in such isolated cases where no primary gene for dRTA is identified.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13730-023-00806-6.

Author contributions PS, SK, BD, SK, and MS managed the patient, reviewed the literature, and drafted the manuscript. SK critically revised the manuscript. All authors contributed to the review of literature, drafting of the manuscript, and approved the final version of the manuscript. SK shall act as the guarantor of the paper.

Funding The authors are grateful to the Indian Council of Medical Research (ICMR) for funding the whole exome sequencing of this child (Grant No. 33/12-2/2019-TF/Rare/BMS). [Grant recipient-Dr Sriram Krishnamurthy].

Declarations

Conflict of interest None stated.

Ethical approval The patient has been enrolled as part of a 3-year research project entitled 'Setting up of registry and targeted exome sequencing in children with renal tubular disorders' approved by the institutional ethics committee (approval number JIP/IEC/2019/491 dated 18 January, 2020: Principal investigator—Dr Sriram Krishnamurthy—corresponding author of the current paper) and informed consent was taken from the parents of the child for publication of this report. The case has not been published so far.

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