Journal of Chemical Health Risks

www.jchr.org

JCHR (2026) 16(1), 2259-2261 | ISSN:2251-6727

Hereditary Distal Renal Tubular Acidosis with Subclinical Hypothyroidism: A Case Report of Slc4a1 Mutation

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(Received: 05 December 2025 Revised: 15 January 2026 Accepted: 10 February 2026)

KEYWORDS

Distal renal tubular acidosis,

SLC4A1 mutation,

Nephrocalcinosis,

growth failure ,

subclinical hypothyroidism

ABSTRACT:

Background: Distal renal tubular acidosis (dRTA) is a rare disorder characterized by impaired acid secretion in the distal nephron. Hereditary variants are infrequent in children, especially those caused by SLC4A1 mutations.

Case Presentation: A 5-year-old developmentally normal girl child born to non-consanguineous parents presented with faltering growth, leg pain, polyuria, polydipsia, and preference for salty foods. Investigations revealed severe metabolic acidosis, hypokalemia, hypercalciuria with alkaline urine and subclinical hypothyroidism. Ultrasound showed bilateral medullary nephrocalcinosis. Suspecting dRTA and primary hyperoxaluria, whole exome sequencing was performed which revealed a homozygous pathogenic variant in the SLC4A1 gene [c.2573C>A (p.Ala858Asp)], confirming autosomal recessive hereditary dRTA. Following treatment with potassium citrate, hydrochlorothiazide and pyridoxine, child showed catch-up growth and improved biochemical parameters during six-month follow-up period.

Conclusion: This case emphasizes the importance of considering hereditary dRTA in children with nephrocalcinosis and growth failure. Genetic confirmation aids in early detection, focused treatment and family counselling.

Introduction

Distal renal tubular acidosis (dRTA) is characterized by impaired urinary acidification, leading to normal anion gap metabolic acidosis, hypokalemia, and growth failure. Hereditary forms are most commonly caused by ATP6V1B1 or ATP6V0A4 mutations; SLC4A1-related disease is less frequent in South Asian children [1]. The SLC4A1 A858D mutation has been described in Indian patients, often in association with hemolytic anemia [2,3]. We present a child with homozygous A858D mutation who manifested nephrocalcinosis and growth retardation but no hematologic involvement, instead demonstrating subclinical hypothyroidism.

Case Report

A 5-year-old girl, firstborn to non-consanguineous parents, presented with poor growth, recurrent leg pain and intermittent abdominal pain for two months. Child had history of polyuria, polydipsia, and preference for salty foods.

Past Medical & Family History: For approximately two years prior to presentation, she had been treated with analgesics for recurrent lower limb pain and received calcium/vitamin supplements for presumed nutritional deficiency, without improvement. There was no family history of renal, metabolic, or endocrine disorders.

Clinical Findings: On examination, height and weight were below the 3rd percentile. There were no signs of rickets, organomegaly, or dehydration. Nutritional intake was below age-recommended requirements.

Investigations revealed Normal anion gap metabolic acidosis , Hypokalemia with Normal renal function. Urine routine showed alkaline urine, hypercalciuria. Abdominal ultrasonography showed normal sized kidneys with bilateral medullary nephrocalcinosis. Whole exome sequencing revealed a homozygous pathogenic variant in the SLC4A1 gene: c.2573C>A (p.Ala858Asp), consistent with autosomal recessive

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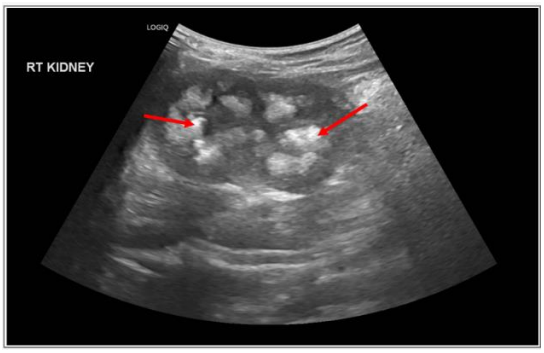
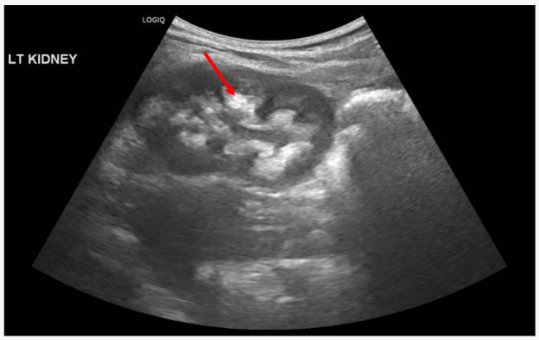
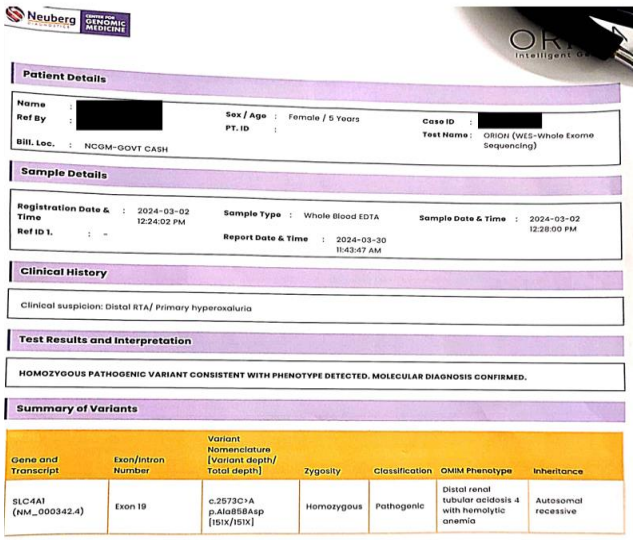
distal RTA. Thyroid function revealed subclinical hypothyroidism (TSH 6.2 mIU/L, normal free T4).Hemogram performed was normal with no evidence of hemolytic anemia.

Therapeutic Intervention: The child was treated for hypokalemia and initiated with oral potassium citrate, hydrochlorothiazide, pyridoxine therapy, and nutritional counselling.

USG KUB SHOWING NEPHROCALCINOSIS






Neuberg Centre for Genomic Medicine

Patient Details

Name : [redacted] Sex / Age : Female / 5 Years Case ID : [redacted]
Ref By : PT. ID : Test Name : ORION (WES-Whole Exome Sequencing)
Bill. Loc. : NCGM-GOVT CASH

Sample Details

Registration Date & Time : 2024-03-02 12:24:02 PM Sample Type : Whole Blood EDTA Sample Date & Time : 2024-03-02 12:28:00 PM
Ref ID 1. : - Report Date & Time : 2024-03-30 11:43:47 AM

Clinical History

Clinical suspicion: Distal RTA/ Primary hyperoxaluria

Test Results and Interpretation

HOMOZYGOUS PATHOGENIC VARIANT CONSISTENT WITH PHENOTYPE DETECTED. MOLECULAR DIAGNOSIS CONFIRMED.

Summary of Variants

Gene and Transcript	Exon/Intron Number	Variant Nomenclature [Variant depth/ Total depth]	Zygosity	Classification	OMIM Phenotype	Inheritance
SLC4A1 (NM_000342.4)	Exon 19	c.2573C>A p.Ala858Asp [151X/151X]	Homozygous	Pathogenic	Distal renal tubular acidosis 4 with hemolytic anemia	Autosomal recessive

PARAMETERS	VALUES	NORMAL RANGE
pH (blood gas)	7.20	7.35–7.45
HCO_3^-	9 mEq/L	22–26
Serum Potassium	2.7 mEq/L	3.5–5.0
Urine Ph	7	<5.5 in acidosis
Urine Calcium	8 mg/kg/day	<4 mg/kg/day
Urine Uric Acid	30.6 mg/kg/day	10–20 mg/kg/day
Urine Oxalate	34.3 mg/day	4–31 mg/day
TSH	8.36 µIU/ml	0.4 – 6.4 µIU/ml
fT4	1.37 ng/dl	0.9-1.7 ng/dl
CBC, RFT, LFT, PTH	Normal	—
Urine glucose, protein	Nil	—

Follow-up and Outcomes

Child had hypokalemia (K-2.3 mmol/L) and was corrected with IV potassium chloride. At six months, she showed catch-up growth (+6 cm height, +1.5 kg weight), resolution of biochemical abnormalities .Thyroid function remained stable at subclinical range and is under periodic monitoring.

Discussion

Distal renal tubular acidosis (dRTA) results in non-anion gap metabolic acidosis, hypokalemia, and failure to thrive. SLC4A1 gene codes for the anion exchanger 1 (AE1) protein.SLC4A1-associated disease is less frequently reported in Indian and South Asian cohorts when compared to ATP6V1B1 and ATP6V0A4 [1]. The A858D mutation in SLC4A1 has been previously described in Indian patients with autosomal recessive dRTA, often associated with hemolytic anemia and hereditary spherocytosis [2,3].In Our case , the child had no hematologic manifestations but instead demonstrated subclinical hypothyroidism.

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Al-Beltagi et al. [4] emphasized the significance of persistent metabolic acidosis in the development of nephrocalcinosis in dRTA. These features were evident in our case, with ultrasound confirming bilateral medullary nephrocalcinosis, a common but under-recognized complication.

In addition to the classic symptoms of hereditary dRTA, such as growth retardation, hypokalemia, hypercalciuria, and medullary nephrocalcinosis-which are direct consequences of chronic metabolic acidosis and impaired urinary acidification, our patient also presented with subclinical hypothyroidism. The co-existence of hypothyroidism in our case has limited documentation in SLC4A1 dRTA literature. However, autoimmune thyroiditis has been reported in association with other forms of RTA, particularly autoimmune or Sjogren's-related dRTA[5]. It's still unclear whether this is due to a chronic illness effect or a coincidental finding.

Therapeutic intervention using potassium citrate, hydrochlorothiazide, and nutritional support led to significant catch-up growth and normalization of biochemical parameters. Early diagnosis and treatment of hereditary dRTA play a key role in preventing irreversible nephrocalcinosis, rickets, and progression to chronic kidney disease[6].

Limitations: Thyroid autoantibody testing was not performed, limiting conclusions about the etiology of hypothyroidism. Longer follow-up duration is needed to clarify the relationship.

Conclusion

This report highlights phenotypic heterogenicity in SLC4A1-related dRTA in a South Asian child, demonstrating nephrocalcinosis and hypothyroidism without hemolytic anemia. Hereditary dRTA due to SLC4A1 mutation is a rare but important differential diagnosis in pediatric patients with growth failure and nephrocalcinosis.

Genetic confirmation supports precision management and gives essential information for family counselling.

Patient Perspective

Parents observed that their child was improving with good appetite and her physical activity improved following symptomatic management. The confirmation of genetic diagnosis provided the parents with clarity and reassurance regarding the cause of their child's condition.

Consent

Written informed consent was obtained from the parents of the child for publication of this case report.

Conflict of Interest

The authors declare no conflicts of interest.

Funding

No external funding was received for this work.

Ethical Approval

Ethical approval was waived for this single case report by the Institutional Ethics Committee.

Acknowledgments

We thank Dr.Sangeetha , Pediatric nephrologist for her valuable inputs in management of the child.We thank the patient and her family for their cooperation.

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