Broadening the differential for Hypocalcemia and Nephrocalcinosis: A case of neonatal renal tubular acidosis

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INTRODUCTION

The endocrinology team often leads the investigation of hypercalcemia in neonates, assessing for causes such as:

- Hyperparathyroidism
- dietary vitamin D or calcium excess
- subcutaneous fat necrosis
- genetic causes (Williams syndrome, congenital lactase deficiency, idiopathic infantile hypercalcemia)

Here we describe an uncommon cause of nephrocalcinosis and hypercalcemia due to renal calcium handling.

PRESENTATION

- Full term 11-day old boy seen by his pediatrician
- History of brief NICU stay for CPAP
- Had not yet regained birthweight at 11 days
- Seen again at 21 days - weight 3.6kg, down from birth weight of 3.81kg
- Poor feeding at home
- Labs in clinic revealed calcium of 16.0mg/dL
- Referred to emergency center (EC)

EMERGENCY CENTER COURSE

- EC labs with hypercalcemia, hypokalemia, acute kidney injury (AKI), appropriately suppressed parathyroid, and normal vitamin D (Figure 1).
- Urine calcium to creatinine ratio >1.29 (urine creatinine below lower limits of lab detection), urine anion gap 25.5
- Started on hyperhydration with 0.45% normal saline
- Feeds temporarily held
- Calcitonin initiated
- Renal ultrasound showed bilateral medullary nephrocalcinosis

Laboratory	Result [Normal Range]
Calcium	**16.2 mg/dL [8.0-10.7]**
Ionized Calcium	**2.31 mmol/L [.95-1.50]**
Parathyroid hormone	<4 pg/mL [6.4-88.6]
Phosphorus	5.7 mg/dL [4.8-8.1]
1,25 Hydroxy Vitamin D	27 pg/mL
25 Hydroxy Vitamin D	30.4 ng/mL
Sodium	142 mmol/L [133-142]
Potassium	2.9 mmol/L [4.0-6.2]
Chloride	112 mmol/L [95-105]
CO2	19 mmol/L [20-28]
BUN	31 mg/dL [2-23]
Creatinine	0.60 mg/dL [0.15-0.40]
Anion Gap	11
Albumin	4.8 g/dL [2.3-4.8]

Fig 1: Laboratory Results at Presentation

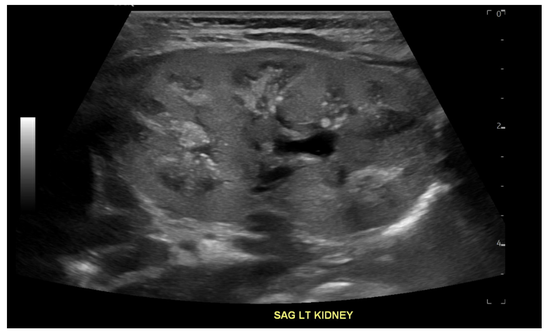

Fig 2: Renal Ultrasound with medullary nephrocalcinosis

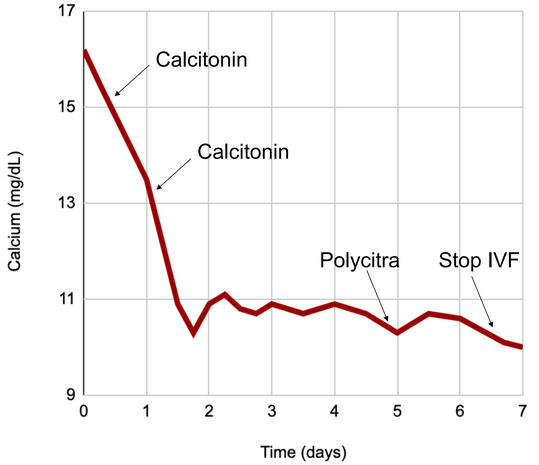

Fig 3: Calcium over time during hospitalization

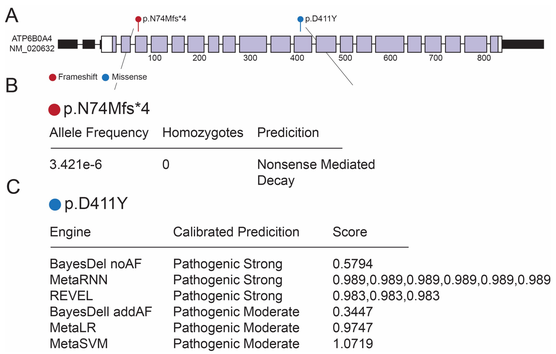

Fig 4: (A) Compound heterozygous variants in the *ATP6V0A4* gene. (B) The maternally inherited variant is not present in a homozygous state in the normal population (gnomAD) and is expected to undergo nonsense mediated decay. (C) The paternally inherited missense variant has been previously reported as pathogenic by multiple clinical labs, and *in silico* tools overwhelmingly agree that it is a damaging variant.

HOSPITAL COURSE

- Worsening hyperchloremia, hypokalemia, and metabolic acidosis on hyperhydration
- Transitioned to custom fluid containing dextrose, potassium acetate, and potassium phosphate
- Remained acidotic. Bicarbonate 14, anion gap 14
- Repeat urine studies with urine anion gap of 32.6
- Concern rose for RTA due to persistent metabolic acidosis with urine anion gap
- Started Polycitra (K & Na citrate/citric acid) with stabilization of hypercalcemia and acidemia (Figure 3). Fluids could then be weaned off.
- Genetics consulted. Trio whole exome sequencing revealed paternally-inherited missense variant at c.1231 (G>T), and maternally-inherited frameshift mutation (c.221del, p.N74Mfs*4) in the *ATP6V0A4* gene (Figure 4).
- Gene associated with autosomal recessive distal RTA, nephrocalcinosis, rickets, poor linear growth, and sensorineural hearing loss[1,2].
- Passed his hearing screen with risk
- Outpatient calcium stable on Polycitra

CONCLUSION

- In infants with hypercalcemia and significant electrolyte derangements, consider distal RTA
- In children requiring large-volume resuscitation, electrolyte abnormalities may not become clear until euvolemic. Repeat urine studies are helpful.
- Specific RTA directed therapy yields resolution of hypercalcemia.

REFERENCES

1. Vargas-Poussou *et al*. Genetic investigation of autosomal recessive distal renal tubular acidosis: evidence for early sensorineural hearing loss associated with mutations in the ATP6V0A4 gene. J Am Soc Nephrol. 2006 May;17(5):1437-43. doi: 10.1681/ASN.2005121305. Epub 2006 Apr 12. PMID: 16611712.
2. Escobar *et al*. Mutations in ATP6V1B1 and ATP6V0A4 genes cause recessive distal renal tubular acidosis in Mexican families. Mol Genet Genomic Med. 2016 Feb 14;4(3):303-11. doi: 10.1002/mgg3.205. PMID: 27247958