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Feature Article

Renal Tubular Dysfunction and Failure to Thrive in Children: A Case Study

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This article has been approved for 2 CPE units. The CPEU insert can be accessed in the Members Only Section of the web site from the CPEU Inserts link.

Case Presentation

This article presents a case study of a young boy with a previous diagnosis of nephrogenic diabetes insipidus and a new question of kidney stones. He was an ex-26 week premie (BW: 853 g) with a history of polyuria and polydypsia since one year of age. He was being managed with thiazide diuretics, which caused significant fatigue according to the parents. After 1 week of treatment the medication was stopped. The parents were seeking further evaluation.

He presented in clinic at 3 and 10/12 years old with failure to thrive (FTT), height of 84.8 cm (3rd percentile), weight of 9.8 kg (< 3rd percentile), Body Mass Index (BMI) of 13.6 (<3rd percentile), polyuria (4-6 liters per day), polydypsia (4 liters per day), and intolerance to milk. The parents reported a very good appetite claiming he ate 4 to 6 times a day and drank water constantly. A 24-hour diet recall suggested an intake of 1700 kcals (150% of RDA) and high sodium (Na) intake. Renal ultrasound showed nephrocalcinosis. Initial labs were all within normal limits and ruled out the diagnosis of nephrogenic diabetes insipidus. A 24-hour urine litholink (an extensive and specific urine analysis) showed severe hypercalciuria, mild hyperoxaluria, hyperuricosuria and very low urinary citrate excretion. The pediatric renal dietitian was consulted to instruct the parents on a high fluid, low Na and low oxalate diet to lessen his risk for stone formation. Plans were made to do further testing to make a differential diagnosis.

Before additional testing could start, the boy was emergently hospitalized with severe hand and foot cramps and stiffening of the arms and legs. Initial labs were significant for hypocalcemia, hypokalemia, hypophosphatemia and hypomagnesemia. 25-hydroxy vitamin D was low but 1,25-dihydroxy vitamin D and parathyroid hormone (PTH) were elevated (Table 1). Consults were obtained from Ophthalmology to detect any signs of cystinosis, Endocrinology to evaluate vitamin D levels and Gastroenterology to evaluate for malabsorption. Nutrition was consulted for a calorie count and evaluation for FTT. His calorie intake initially was poor, but once electrolyte replacement began his appetite returned and was eating adequately. FTT due to inadequate calorie and protein intake was ruled out. Ophthalmology ruled out cystinosis. Endocrinology found normal parathyroid function but a significantly delayed bone age of 2 years old. Gastroenterolgy determined there was no malabsorption.

A working diagnosis of Bartter Syndrome was made, but the parents refused further genetic testing to determine the variant of Bartter

Table 1
Laboratory Values

	Reference Range	Clinic Visit	Hospital Admit	Hospital Discharge	2 Wks Post D/C	10 Wks Post D/C
Na (mmol/L)	135-145	136	143	134	137	140
K (mmol/L)	3.5-5.2	3.6	2.4	3.9	3.3	4.5
Cl (mmol/L)	95-109	102	104	106	101	102
Ionized Ca (mmol/L)	1.14-1.32	N/A	0.7	1.16	1.23	N/A
Mg (mg/dL)	1.6-2.6	1.7	1.3	2.1	2.1	2.1
P (mg/dL)	4.5-6.5	5.1	4.1	6.0	4.98	6.3
Albumin (g/dL)	3.5-5	4.1	3.2	N/A	3.6	4.4
25-hydroxy vitamin D (ng/mL)	20-57	N/A	7	N/A	N/A	N/A
1, 25 vitamin D (pg/mL)	15-75	N/A	128	N/A	N/A	N/A
PTH (pg/mL)	15-75	N/A	283	N/A	20	N/A

N/A = not available

Syndrome. A second diagnosis of nutritional vitamin D deficiency was also made based on his history of milk intolerance and low 25-hydroxy vitamin D. Medications during his hospital stay included indomethacin, spironolactone, calcium carbonate, potassium chloride (KCl), ergocalciferol, magnesium oxide, neutra-phos, and IV saline fluids. Prior to discharge the neutra-phos was discontinued as his serum phosphorous (P) normalized. All other medications and mineral/vitamin supplementation were continued at discharge. He was also put on a high Na, high potassium (K) diet and high fluid diet. No particular level of Na or K was identified, but rather, foods high in Na and K content were reviewed. The parents identified favorites of the child and were advised to increase the portions and frequency. The family was Korean and used many high Na sauces. This practice was encouraged. Finally a minimum goal of at least 2 liters of fluid per day was advised.

Table 2
Anthropometrics

	Clinic Visit	Hospital Admit	2 Wks Post D/C	10 Wks Post D/C
Height (cm)	84.8	86.36	87.4	89.4
Weight (kg)	9.8	9.8	11.1	11.3
BMI	13.6	13.1	14.5	14.1
BMI percentile	< 3rd	<3rd	15th	8th

Within one month after discharge, spironolactone and calcium carbonate were discontinued. The ionized calcium (Ca) was rising rapidly and the child was eating yogurt and cheese daily. He continued on indomethacin, ergocalciferol, KCl, and magnesium oxide. He began to achieve catch-up growth in height and weight. BMI increased from less than the 3rd percentile to the 8th percentile by 10 weeks post discharge (Table 2).

Discussion

This case report is an excellent example of how disturbances within the renal tubules can clinically present as FTT. This particular patient was diagnosed with Bartter Syndrome which led to excessive excretion of K, Na, Ca, and water. His secondary diagnosis of vitamin D deficiency exacerbated his condition due to insufficient absorption of Ca and P. The initial dietary intervention of salt and oxalate restriction, implemented to prevent kidney stones, may have exacerbated the condition by increasing urine output further. Bartter Syndrome is comprised of several closely related disorders of renal electrolyte transport. It is most often characterized by Na, K and chloride (Cl) wasting, hypokalemic metabolic alkalosis, hyperreninism and hyperaldosteronism. There are 5 variants of the syndrome, Types I through V, with variations in the types and severity of electrolyte disturbances that can occur. Detailed descriptions of these variants go beyond the purpose of this discussion; however, excellent reviews of the variants can be

Table 3
Renal Tubular Disorders that can Present with Failure to Thrive

- Fanconi Syndrome (proximal tubular dysfunction)
- Chronic Chloride Deficiency (metabolic alkalosis due to dietary chloride deficiency)
- Primary Proximal Renal Tubular Acidosis
- Distal Renal Tubular Acidosis
- Nephrogenic Diabetes Insipidus
- Bartter Syndrome
- Gitelman Syndrome
- Pseudo-Bartter Syndrome

found in Shaer (1), Proesman (2) and Unwin (3).

It has been established that defective sodium chloride (NaCl) transport at different segments of the distal tubule leads to the variants of Bartter Syndrome (1). The primary abnormality is defective Cl re-absorption in the thick ascending loop (TAL) of the loop of Henle (1). This leads to increased delivery of NaCl to the distal tubule which increases K and hydrogen losses leading to hypokalemic metabolic alkalosis and impaired urine concentrating. Another consequence of decreased Cl re-absorption is decreased Ca and magnesium (Mg) re-absorption leading to hypercalciuria and increased Mg losses (1). Clinically, the patient almost always presents with polydypsia, polyuria and FTT. Most patients presenting with Bartter Syndrome are pediatric, however, it has also presented in adult patients whenever damage to the tubules occur. Pseudo-Bartter syndrome presents more frequently in adults if there is abuse of thiazide and loop diuretics. These diuretics act at the site of Cl re-absorption and inhibit it, leading to excess Cl excretion. It differs from Bartter's because there is no renal tubular dysfunction. Once the diuretics are stopped and excessive excretion of Cl and Na ceases, the metabolic abnormalities resolve (4).

Of particular interest is the association with FTT and growth failure in conjunction with adequate calorie and protein intake. This pattern is more commonly seen with other pediatric renal disorders that affect the tubules' ability to reabsorb electrolytes, cause excessive excretion of electrolytes, or lead to inadequate re-absorption/excessive excretion of water (5). Table 3 lists some of the other disorders affecting the renal tubules. Although the tubular dysfunction will differ among those listed, the common overall features are the loss of one or more nutrients (Na, K, Cl, Ca, P, Mg and/or water) and FTT is a presenting factor at the time of diagnosis. In some disorders, FTT occurs despite evidence of adequate calorie and protein intake (e.g. Bartter, Gitelman, Chronic Chloride Deficiency and Pseudo-Bartter) (6). In other tubular disorders such as Renal Tubular Acidosis and Fanconi, FTT is accompanied by either no anorexia or mild to severe anorexia (7, 8, 9).

No clear evidence has been found to explain the definitive link between electrolyte and/or fluid wasting and FTT. Renal K wasting has been implicated in Bartter Syndrome as a growth depressing factor (10, 11, 12). However, only experimental studies have demonstrated that K depletion plays a role in growth retardation as it is accompanied by reduced growth hormone (GH), reduced response to GH releasing factors and reduction of insulin growth factor (IGF) (13, 14). The importance of K in the proper utilization of carbohydrate in insulin release and in growth is also well known but the mechanisms are unclear (1). In an early study, correcting the K deficiency in children with Bartter Syndrome did not always correct growth failure, suggesting other mechanisms are also involved (15). A recent case report of a girl with primary aldosteronism whose growth failure was treated successfully with K supplementation concluded that "serum electrolytes should be included in the evaluation of children with impaired growth" (16).

The hypophosphatemia seen in some tubular disorders results in severe bone changes, bone age delay, and poor growth (9). Good catch-up growth has been reported with P supplementation and normalizing of serum phosphorous (17).

Metabolic acidosis, accompanied by negative Na balance, occurs in numerous tubular dysfunction syndromes such as renal tubular acidosis, and has been identified as an important determinant of FTT (8, 9). Acidosis is known to interfere with major aspects of the GH-IGF axis and ultimately results in the blunting of GH release in children (7). Metabolic acidosis is not a feature of Bartter syndrome.

It is known that successful GH therapy in children with chronic kidney disease (CKD) requires correction of metabolic acidosis and adequate calorie and protein intake (18). GH utilization also requires an adequate nutrient supply (18), and in cases of the various tubular disorders, the supply of minerals, particularly Na, K, Cl, Ca, P and/or Mg is impaired. Inadequate supply of minerals may not only prevent synthesis of IGF, but also impairs growth. Therefore, sufficient supply of the minerals lost by the kidneys may be crucial to providing catch-up growth and resolution of FTT (19, 20).

One of the mainstays of treatment common to the variety of tubular disorders is to provide supplementation of the minerals lost. NaCl, KCl, Ca, P and Mg supplements were all utilized at the initiation of treatment in this case study. Vitamin D also was supplemented, however vitamin D deficiency was a secondary diagnosis not related to Bartter Syndrome. However, it did exacerbate the condition. Also, osteopenia is common with prematurity and may have intensified his Ca and P deficit further. Usual treatment for Bartter Syndrome utilizes indomethacin to treat elevated urinary prostaglandins. Elevated prostaglandins

can lead to suppression of water re-absorption in the collecting duct and NaCl transport in the TAL of the loop of Henle (1). Indomethacin acts to reduce renal excretion of prostaglandin and attenuate the hyperreninism and hyperaldosteronism seen with Bartter Syndrome (1). In addition, indomethacin decreases polyuria, salt wasting and hypokalemia (1).

Finally, appropriate dietary intervention is a part of treatment. Encouraging a diet that is mineral dense, particularly in the minerals that are being wasted is important. The Na restricted diet initially advised at the patient's first clinic visit (i.e. due to the working diagnosis at that time of kidney stones and nephrocalcinosis) was the wrong advice to give in light of the subsequent diagnosis of Bartter Syndrome! Instead, a high Na diet was implemented during the hospitalization and was included in the discharge diet counseling. Indeed, the NaCl supplementation initially provided could be discontinued because the child was able to increase Na content in his diet easily to the amount necessary to normalize his biochemistry. An increased K diet was also encouraged; however, additional KCl supplementation was still required.

Conclusion

Defects in the re-absorption and/or excessive excretion of minerals and water by the proximal and/or distal renal tubules can lead to FTT in children. This growth failure may or may not be accompanied by inadequate calorie and protein intake.

Pediatric renal dietitians working with children presenting with FTT need to also consider renal tubular dysfunction as a cause of FTT and adjust diet interventions accordingly. By far, most children presenting to a pediatric nephrologist have CKD as a reason for FTT. Strategies for treatment should include correction of acidosis, growth hormone therapy, adequate nutrition and control of Ca and P levels. However, children with renal tubular dysfunction may have no signs of CKD initially, may be eating quite well and yet present with significant FTT. Diet therapy should be aimed at maintaining a higher fluid intake and high mineral diet in these children. ◆

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