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Approach to Pediatric Renal Tubular Acidosis

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Introduction:

Hello everyone! My name is Shadi Sadeghian and I am a second year medical student at McMaster University. Today we are going to be talking about pediatric renal tubular acidosis. I would like to thank Dr. Charushree Prasad, pediatric nephrologist and assistant professor at McMaster Children's Hospital, for reviewing this episode.

Case:
Let's start with a case. You're doing an elective on the peds nephrology service, and you meet Sid, an
18-month-old baby boy who was referred to your team with polydipsia, polyuria, and failure to thrive – while he was at the 50th percentile at his 12-month visit, at 15 months he had dropped from his growth curve. Sid has required multiple diaper changes during the night, there are no other urinary symptoms. He has been eating a variety of solid foods and drinking milk, and has been healthy up until now, with normal pregnancy and delivery. On exam, he appears cachectic but otherwise unremarkable. Laboratory data are notable for a low venous pH of 7.2, low bicarbonate, hypokalemia, and hypophosphatemia. His general pediatrician also ordered urine studies, which show glucosuria on urine dipstick, increased potassium excretion, and low molecular weight proteinuria, which generally indicates tubular protein loss and is different from albuminuria (which reflects glomerular losses).

Spoiler alert, but after a thorough work up, Sid ends up being diagnosed with a Renal tubular acidosis (RTA), which is a non-anion gap hyperchloremic acidosis that is subdivided into 4 types, based on the specific tubular dysfunction at play. But before we delve into what exactly RTA is, and what subtype our friend Sid has, let's take a step back and take a journey through the nephron to review normal renal physiology.

Overview of Normal Renal Physiology: (can be trimmed)

Kidneys play a pivotal role in maintaining the acid-base balance of body along with lungs, and they do so by reabsorbing filtered bicarbonate and removing excess hydrogen ions. The nephrons are the functional unit of the kidney that are responsible for this fine-tuning process.

As filtrate (or early urine) passes through the glomerulus, it is greeted by its first stop in the journey of the nephron, which is the proximal convoluted tubule. One of the goals of the proximal tubule is to reabsorb the bicarbonate that was filtered in the glomerulus. This happens indirectly, as bicarbonate enters the tubular cells, gets converted into water and CO2, and then re-catalyzed to bicarbonate and hydrogen ions. The bicarbonate that is re-created in this process is transported back into the blood. For every bicarbonate that is reabsorbed, we have a hydrogen ion that is secreted into the filtrate.

The next stop is the descending and ascending loop of Henle. This region is not responsible for acid-base fine tuning, but rather pumping out ions and solutes as well as drawing out water. So, as our filtrate passes by, it becomes more concentrated.

Now that we have our concentrated filtrate, its next stop is the distal convoluted tubule. This is where the nephron does further fine tuning and secretes hydrogen ions. Normal renal hydrogen ion secretion involves 3 steps: Step 1) reabsorption of sodium to create a negative gradient in the tubular lumen, Step 2) excretion of H+ by ATPase, Step 3) a specialized epithelium to prevent H+ ions from diffusing back out of the tubular lumen. This means our filtrate is now void of almost all bicarbonate, and full of hydrogen ions, which are buffered by titratable acids that are present in the filtrate. Another important function of the DCT is further removal of sodium and chloride from the filtrate. Aldosterone acts on the alpha intercalated cells of the DCT to increase the rate of this by increasing the synthesis and mobilization of the sodium channels. This increased sodium absorption in turn leads to potassium excretion into the filtrate. When aldosterone binds to the mineralocorticoid receptor, sodium resorption into the body occurs, which is needed for hydrogen ions to in turn be secreted. This then causes potassium excretion into the filtrate, thus maintaining electroneutrality. Essentially, by the time our filtrate gets to the collecting ducts, there should be water, waste products, potassium, and hydrogen left in it.

Just to summarize, acid-base handling in the renal tubule can be broken down into **two stages**: Proximal reabsorption of filtered bicarbonate, and distal acidification of the urine.

<u>Clinical Approach to NAGMA</u> (can do without UAG – last paragraph)

RTA is a relatively rare disorder. However, by definition it is a non-anion gap metabolic acidosis or NAGMA, and NAGMA has a very broad differential.
Let's go back to basics first. When we talk about NAGMA, we are referring to a state of acidosis, so a pH<7.45 on a blood gas, in the context of an anion gap greater than 12. And remember, to identify that we are dealing with a metabolic acidosis, we have low pH as well as low serum bicarbonate, suggesting a base deficit. For a detailed review on how to calculate an anion gap and more about acid-base disturbances, check out the "Approach to Acid-Base Disturbances" episode on PedsCases.

If metabolic acidosis is tentatively identified by a low total CO2 on an electrolyte panel measurement, an arterial or venous blood gas sample may be needed to differentiate metabolic acidosis from compensated respiratory alkalosis, since a low bicarbonate level may be observed in both conditions. If the patient has a simple metabolic acidosis, then the patient will be acidemic with a pH <7.35, and if the patient has respiratory alkalosis with compensated metabolic acidosis, the patient is alkalemic with a pH >7.4.

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Once the diagnosis of a metabolic acidosis has been confirmed, serum electrolyte values are used to determinate the serum anion gap, which is the difference between measured cations and measured anions. As a refresher, Serum AG = Na – (Cl + HCO3). Remember, the anion gap can be underestimated in children with hypoalbuminemia.

Let's say we've reviewed the blood work, and the anion gap is normal, and we need to figure out what's going on here. A diagnostic evaluation that includes serum or plasma electrolytes, calculation of the anion gap, and elements from the history and physical examination are usually sufficient to determine the cause of the metabolic acidosis and guide therapy. When thinking about our broad differentials for NAGMA, we can think of three groups of Etiologies: GI losses, chloride intoxication, and renal losses. Three groups of causes of NAGMA include:
GI losses – diarrhea, surgical drains, ureteral diversion to bowel, cholestyramine
Chloride intoxication – normal saline (common), HCl or chloride gas intoxication (rare)
Renal losses – Renal tubular acidosis types 1, 2, 4
Have you HEARD OF a mnemonic to remember causes of NAGMA? Well, one mnemonic is, in fact "HEARD OF" – Hypoaldosteronism, extra chloride, acetazolamide, RTA, Diarrhea, Ostomies, and Fistulae. Think about that when someone asks if you've HEARD OF NAGMA before.

Patients with metabolic acidosis and normal anion gap generally have an underlying disorder that results in a loss of bicarbonate. Most pediatric cases with normal anion gap are due to losses of bicarbonate from the gastrointestinal tract and are typically diagnosed based on a history of diarrhea or abnormal drainage from the small bowel or pancreas.

If the etiology of the normal anion gap remains unclear, a urine anion gap may be useful. This is calculated by the formula: Na+K-Cl. In the presence of metabolic acidosis, a positive value for urine anion gap is indicative of relatively low excretion of the titratable acid ammonium (NH4+), which is indicative of RTA subtypes. Such as is seen in distal (type 1) and hypoaldosteronism (type 4) renal tubular acidosis. Conversely, a negative value is consistent with intact urinary ammonium excretion as seen in children with metabolic acidosis due to proximal (type 2) renal tubular acidosis and gastrointestinal losses. This is because in a proximal RTA, acidification of urine is intact, because the function of the PCT is normal. One way to remember this is "Ne-GUT-ive" – a negative urine anion gap points more towards GI losses of bicarbonate.

RTA Pathophysiology and Subtypes

Now that we've discussed our approach to NAGMA and we have arrived at a working diagnosis of RTA for our case, let's now understand the subtypes of RTA in order to better understand what is going on with our patient Sid.

We learned that the major functions of the kidneys in acid-base homeostasis are to excrete H and reabsorb HCO3. Failure to perform these functions results in HCO3 wasting or diminished acid secretion, leading to renal tubular acidosis (RTA). It is a non-anion gap hyperchloremic metabolic acidosis that occurs in the presence of relatively preserved GFR.

The precise pathophysiological mechanism underlying the disorder varies across RTA sub-types: distal (type I), proximal (type II), and hyperkalemic (type IV) RTA. Type III is rare and will not be discussed. I know there's a lot of nomenclature involved here, so here is a mnemonic to help you remember them: D comes before P in the alphabet, so type 1 is distal RTA, type 2 is

proximal RTA. But to simplify, I will only be using the terms distal, proximal, and type IV moving forward.

In children, renal tubular acidosis (RTA) is due to either an inherited or acquired defect that affects the kidney's ability to absorb filtered bicarbonate or excrete ammonia or titratable acid.

Let's start with talking about proximal RTA. Proximal RTA is caused by a reduction in proximal bicarbonate reabsorption, which causes a fall in the plasma bicarbonate. In this case, our distal convoluted tubule is functioning just fine, which means our urine is being acidified normally. So, urine pH is likely normal. Proximal RTA can be either an isolated tubular defect, but it's more commonly as a component of a generalized proximal tubular losses called Fanconi syndrome. Same name alert! This is different from Fanconi anemia, which is a hematological disorder. Fanconi syndrome is characterized by proximal RTA (and thus, inappropriate loss of bicarb), phosphaturia, renal glucosuria (with a normal plasma glucose concentration), aminoaciduria, and tubular proteinuria. Causes for Fanconi syndrome can be either genetic or acquired. Acquired causes include heavy metals, and medications such as aminoglycosides, cisplatin, and valproic acid. Several genetic causes of Fanconi appear during infancy, with infantile form of cystinosis being the most common. Cystinosis is a lysosomal storage disorder that is characterized by accumulation of cystine in all organs, which leads to dysfunction of PCT cells.

Proximal RTA can also occur as a transient developmental problem in neonates. Commonly, term infants have a normal mild RTA, with serum bicarbonate concentrations 20 to 24 mmol/L, and preterm infants may have values as low as 15 mmol/L. This is a transient abnormality of bicarbonate resorption that improves progressively during infancy.

Let's move on and discuss distal RTA. So distal RTA involves impaired distal acid secretion that results in an inability to excrete the daily acid load. This progressive hydrogen ion retention leads to a fall in plasma bicarbonate concentration that is accompanied by an abnormally high urine pH (greater than 5.5). The etiology for type I RTA can be genetic or acquired. Genetic primary causes of distal RTA include mutations of genes that directly affect membrane transport proteins such as the chloride-bicarbonate exchanger or subunits of the H-ATPase pump – either dominant or recessive, recessive being a more severe phenotype. Acquired causes of distal RTA often have medications as the culprit. For instance, amphotericin B can result in reversible distal RTA, and lithium can cause an incomplete distal RTA. Characteristically, this type of RTA presents with hypokalemia as potassium is lost in the urine as a cation replacement for hydrogen. Some other key distinguishing features of distal RTA would be the presence of low citrate in the urine, which predisposes to increased precipitation of calcium in the kidney leading to nephrocalcinosis or kidney stones.

Lastly, we have type 4 RTA, typically due to aldosterone deficiency or resistance. If we think back to our RAS physiology, less aldosterone leads to less sodium retention, which leads to less hydrogen being excreted in the urine. It is uncommon in children and is usually due to either aldosterone deficiency or tubular resistance to the action of aldosterone, also called pseudohypoaldosteronism. Hyperkalemia is a key feature of this type of RTA because aldosterone is the major hormone that promotes potassium excretion. Other clinical features in children with hypoaldosteronism may include failure to thrive and hyponatremia because of sodium loss.

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Hypoaldosteronism in children is more likely to be due to drugs that impair aldosterone release or function. These include heparin, nonsteroidal antiinflammatory agents, angiotensin inhibitors, and potassium sparing diuretics. However, it can also be due to inherited disorders, such as Congenital adrenal insufficiency or genetic defects of aldosterone receptors or Enac sodium transporter function. As a clinical pearl, when working up hyperkalemia with normal GFR, think about type 4 RTA and pseudohypoaldosteronism.

An example of a genetic syndrome causing type IV RTA via pseudohypoaldosteronism is Gordon's syndrome. This syndrome can be caused by several different mutations that can lead to unregulated sodium reabsorption in the distal tubule leading to significant hypertension. This means there's less sodium left in the filtrate when it reaches the collecting duct. This results in reduced driving force for aldosterone-mediated potassium and hydrogen ion secretion, leading to hyperkalemia and acidosis. Gordon syndrome is generally easily treated by use of a thiazide diuretic to reverse the dysregulated sodium absorption in the distal tubule.

Now that we know the bare bones of what each type of RTA involves, let's briefly discuss its management and our approach to helping our patient Sid.

Management of RTA

Before discussing the management of RTA, let's go back to our case.
Sid is our 18-month-old baby male who presented with failure to thrive. Bloodwork completed, shows low potassium, low phosphate and elevated creatinine. History of polydipsia - drinking up to 5 L of water per day, and polyuria - soaking wet diapers that needed to be changed multiple times overnight. He has had normal development to date, and normal vision and hearing, and no dysmorphic features.

Labwork reveals a venous pH of 7.20, low bicarb of 15, a high chloride of 114, and a low potassium of 2. His creatinine is also elevated at 43. Sid's urine studies show low molecular weight proteinuria, with a high urine beta-2 microglobulin level, generalized amino aciduria, and glucosuria, despite normal serum glucose. To summarize, Sid has loss of various ions and molecules in the urine, a hyperchloremic NAGMA, and low serum bicarbonate. You remember reading about Fanconi syndrome and proximal RTA, and suspect this might be the cause of Sid's presentation. Given lack of medications in Sid's history to suggest acquired causes, you suggest to your staff that genetic studies be conducted. Your staff agrees and commends you on your diagnostic acuity. The results show that Sid has cystinosis, causing dysfunction of proximal tubular cells.

Therapy for proximal RTA includes bicarbonate supplementation, as high as 10 mEq/kg per day or more, titrated as needed to correct the acidosis. Additional therapy involves correcting any other electrolyte abnormalities that may be present, particularly if we have mass tubular dysfunction as in Fanconi syndrome. The clinical presentation of this type of RTA almost always involves symptoms caused by dehydration and tubular loss of all electrolytes. Therapy therefore focuses correction of acidosis, followed by acute management of other electrolyte abnormalities such as marked hypokalemia, with supplementation via potassium citrate and potassium phosphate. However, we have to remember that RTA's generally present as part of a larger genetic syndrome. In Sid's case, management was focused at management of cystinosis, which we discussed is abnormal accumulation of cystine in tissues. Management of this condition includes cystamine supplementation to adequately metabolize cystine molecules. If there's an acquired cause, the mainstay of therapy is limiting exposure to the offending agent.

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Distal RTA usually is also treated successfully with added alkali (bicarbonate) in low doses, ranging from 1 to 3 mEq/kg per day. Such therapy usually corrects the metabolic acidosis, but again, may not correct extra-renal abnormalities if a larger genetic syndrome is at play. In the acquired types, correction of the underlying cause or stopping the associated drug therapy results in improvement. We also need to monitor for nephrocalcinosis and stones. Sometimes distal RTA is also associated with hearing loss, and patients need screening for this.
For Type IV RTA, the mainstay of therapy is to treat symptomatically with potassium binders such as keyexelate and bicarbonate supplementation. Low potassium diet may also provide symptomatic relief, since hyperkalemia is pathognomonic of type IV RTA. As with proximal and distal RTA, treating the over-arching cause of the RTA is paramount. For instance, in Gordon's syndrome which is a type of pseudohypoaldosteronism we discussed previously, thiazide diuretics are excellent at mitigating the excess sodium reabsorption that occurs in the distal tubule.

Aside from the above, therapy is mainly supportive in nature. As we saw with baby Sid, another common effect of RTA is failure to thrive. In this case, nutritional supplements or G-tube feeding may be required in order to meet metabolic demands. Fluid replacement may also be indicated if there is clinical evidence of dehydration. Close monitoring of patients and regular follow up is required to provide adequate supportive care. In providing alkali therapy, the treatment goal is to achieve and maintain a normal serum bicarbonate level (22 to 24 mmol/L). Frequent monitoring is extremely important in pediatrics, because rapid growth can lead to changes in alkali therapy requirements. All of these patients need to be closely followed by pediatricians and pediatric nephrologists and generally require the care of a multidisciplinary team including a dietitian and pharmacist.

Thanks for listening!

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