Renal Tubular Disorders

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Learning Objectives

• Understand the basic mechanisms of renal tubular electrolyte and acid-base handling.
• Recognize and plan the diagnosis of the more common renal tubular disorders in children.
• Initiate treatment of common renal tubular disorders in children.

Nephrology is Fun!

Berne & Levy, Physiology, 6th Ed., 2010

Nephrology is Fun!

Berne & Levy, Physiology, 6th Ed., 2010

Nephrology is Fun!

Nephrology is Fun!

Functions of the Kidney
- Waste removal
- Fluid homeostasis
- Electrolyte homeostasis
- Acid-base homeostasis
- Blood pressure regulation
- Erythropoiesis
- Gluconeogenesis

What's the deal with kidneys?

Nephrons – The Functional Units of the Kidney

First Question…

One Approach to Metabolic Acidosis
- **High anion gap**
  - Methanol
  - Uremia
  - DKA
  - Paraldehyde
  - Isoniazid
  - Lactic acidosis
  - Ethylene glycol
  - Salicylate

- **Normal anion gap**
  - ‘HARD-UP’
  - Hyperalimentation
  - Acetazolamide
  - RTA
  - Diarrhea
  - Ureteroenteric fistula
  - Pancreatic-duodenal fistula
Renal Distal Tubular Acidosis

Diagnosis of Distal (Type 1) Renal Tubular Acidosis

- **Diagnosis**
  - Failure to thrive
  - Normal anion-gap metabolic acidosis
  - Hypokalemia
  - Urine pH > 5.5
  - Positive urinary anion gap
    - (Na-K - Cl) > 0
  - Nephrocalcinosis

Urine pH in Patients with Distal RTA

Distal (Type 1) Renal Tubular Acidosis

Medullary Nephrocalcinosis on X-ray
Medullary Nephrocalcinosis on Ultrasound

Chan, J Pediatr 1983


Distal (Type 1) Renal Tubular Acidosis

- Treatment
  - Potassium citrate/citric acid
  - Usual require 1-3 mEq/kg/day
  - Oral solution: 2 mEq/mL
  - Powder: 30 mEq/pkt
  - Tablet: 5, 10, 15 mEq/tab

- Discontinuation of offending agent

Treatment of Distal (Type 1) Renal Tubular Acidosis

<table>
<thead>
<tr>
<th>Potassium content in food</th>
<th>Approximately 100 g of potassium</th>
<th>Percent of potassium</th>
<th>Nutritional significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>banana</td>
<td>45 mEq</td>
<td>0.5%</td>
<td>10%</td>
</tr>
<tr>
<td>mushroom (1 tbsp)</td>
<td>640 mg</td>
<td></td>
<td>250%</td>
</tr>
<tr>
<td>broccoli (1 cup)</td>
<td>320 mg</td>
<td></td>
<td>30%</td>
</tr>
<tr>
<td>liver (liver)</td>
<td>380 mg</td>
<td></td>
<td>10%</td>
</tr>
<tr>
<td>lemon (1 cup)</td>
<td>240 mg</td>
<td></td>
<td>10%</td>
</tr>
<tr>
<td>orange (2 cups)</td>
<td>480 mg</td>
<td></td>
<td>30%</td>
</tr>
<tr>
<td>potato (1 cup)</td>
<td>250 mg</td>
<td></td>
<td>10%</td>
</tr>
<tr>
<td>tomato (1 cup)</td>
<td>405 mg</td>
<td></td>
<td>30%</td>
</tr>
<tr>
<td>kidney (1 cup)</td>
<td>650 mg</td>
<td></td>
<td>25%</td>
</tr>
</tbody>
</table>

History of Proximal (Type 2) Renal Tubular Acidosis

History of Proximal (Type 2) Renal Tubular Acidosis

Soriano et al, Pediatr Res 1967

Causes of Proximal (Type 2) Renal Tubular Acidosis

- Congenital
  - Cystinosis
  - Tyrosinemia
  - Galactosemia
  - Wilson’s disease
  - Lowe’s syndrome
  - Carbonic anhydrase deficiency
  - Mitochondrial disease

- Acquired
  - Valproic acid
  - Aminoglycosides
  - Carboplatin
  - Ifosfamide
  - Acetazolamide
  - Cyanotic congenital heart disease
  - Multiple myeloma
  - Amyloidosis

Diagnosis of Proximal (Type 2) Renal Tubular Acidosis

- Diagnosis
  - Failure to thrive
  - Normal anion-gap metabolic acidosis
  - Hypokalemia
  - Urine pH <5.5
  - Glucosuria, aminoaciduria, phosphaturia
  - Vitamin D deficiency, rickets

Diagnosis of Proximal (Type 2) Renal Tubular Acidosis

Urine pH in Patients with Proximal RTA


Proximal (Type 2) Renal Tubular Acidosis

Lowe’s Syndrome

Rickets

http://lowesyndrome.org
http://radiopaedia.org/articles/rickets
Treatment of Proximal (Type 2) Renal Tubular Acidosis

- Treatment
  - Sodium citrate solution
  - Sodium bicarbonate
  - 650mg tablets
  - Usually require high doses, >10-15 meq/kg/day
  - Discontinuation of offending agent

History of Hyperkalemic (Type 4) Renal Tubular Acidosis

Discovery of Aldosterone

Causes of Hyperkalemic (Type 4) Renal Tubular Acidosis

- Congenital
  - Addison’s disease
  - Congenital adrenal hyperplasia (21-OH)
  - Isolated aldosterone deficiency
  - Pseudohypoaldosteronism type 1
  - MR receptor mutation (AD)
- Acquired
  - Diabetes mellitus
  - Interstitial nephritis
  - Obstructive uropathy
  - Calcium oxalate
  - ACEI/ARB
  - NSAIDs
  - Transient

Diagnosis of Hyperkalemic (Type 4) Renal Tubular Acidosis

Type 3 RTA???

- Initially thought to be a distinct entity.
- Combined proximal and distal defects.
- Many believe that it is transient proximal bicarbonate wasting in infants with distal RTA.
- It most likely will not be on your exam.
Diagnosis of Renal Tubular Acidosis

<table>
<thead>
<tr>
<th>Test</th>
<th>Proximal RTA</th>
<th>Distal RTA</th>
<th>Type II RTA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma K+</td>
<td>Normal/low</td>
<td>Normal/low</td>
<td>High</td>
</tr>
<tr>
<td>Urine pH</td>
<td>&lt; 5.6</td>
<td>&gt; 5.5</td>
<td>&lt; 5.5</td>
</tr>
</tbody>
</table>
| Urine 
HCO3- | Low | Positive | Positive |
| Fractional 
HCO3- excretion | > 10-15% | > 15% | < 15% |
| Urine 
Cl | Normal | Normal | Normal/low |
| UFP-CO2 | Common | Absent | Absent |
| Urine 
PO2 | Common | Absent | Absent |

Urinary Cl: Normal 15 meq/L

- Gastrointestinal losses
- Emesis
- Gastric aspiration
- Villous adenoma
- Cystic fibrosis
- Congenital chloride diarrhea
- Post hypercapnia
- Proximal diuretic use

Urinary Cl: > 20 meq/L

- High blood pressure
  - RAS
  - Adrenal adenoma
  - Renin-secreting tumor
  - Cushing syndrome
  - CAH (17a, 11B)
  - Licorice ingestion
  - Liddle syndrome

Renal Sodium Handling

- Alkali supplementation
- Current diuretic use
- Bartter syndrome
- Gitelman syndrome

Next Question…

Approach to Metabolic Alkalosis

- Urinary Cl <15 meq/L
  - Gastrointestinal losses
  - Emesis
  - Gastric aspiration
  - Villous adenoma
  - Cystic fibrosis
  - Congenital chloride diarrhea
  - Post hypercapnia
  - Proximal diuretic use

- Urinary Cl >20 meq/L
  - High blood pressure
  - RAS
  - Adrenal adenoma
  - Renin-secreting tumor
  - Cushing syndrome
  - CAH (17a, 11B)
  - Licorice ingestion
  - Liddle syndrome

- Normal BP
  - Alkali supplementation
  - Current diuretic use
  - Bartter syndrome
  - Gitelman syndrome

Having Fun Yet?
Bartter Syndrome

- Salt-wasting tubulopathies
- Autosomal recessive
- Mutations in salt-handling channels in loop of Henle
  - NKCC, ROMK, CLCN/Barttin
- Presentation
  - Infant/child
  - Polyhydramnios, prematurity
  - Polyuria, dehydration, FTT
  - Nephrocalcinosis

Bartter Syndrome Types

<table>
<thead>
<tr>
<th>Type I Bartter Syndrome</th>
<th>Type II Bartter Syndrome</th>
<th>Type III Bartter Syndrome</th>
<th>Type IV Bartter Syndrome</th>
<th>Type V Bartter Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inheritance</td>
<td>AR</td>
<td>AR</td>
<td>AR</td>
<td>AR</td>
</tr>
<tr>
<td>Affected tubular region</td>
<td>TAL</td>
<td>TAL + CCD</td>
<td>TAL + DCT</td>
<td>TAL</td>
</tr>
<tr>
<td>Gene</td>
<td>SLC12A1</td>
<td>KCNJ1</td>
<td>CLCN/Barttin</td>
<td>CASR</td>
</tr>
<tr>
<td>Onset</td>
<td>Prenatal, postnatal</td>
<td>Prenatal, postnatal</td>
<td>Variable</td>
<td>Variable</td>
</tr>
<tr>
<td>Urine PGE 2</td>
<td>Very high</td>
<td>Very high</td>
<td>Slightly elevated</td>
<td>Elevated</td>
</tr>
<tr>
<td>Hypokalemic metabolic alkalosis</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
</tr>
</tbody>
</table>

Features

- Polyhydramnios, prematurity, nephrocalcinosis, dehydration, hyposthenuria, polyuria, failure to thrive

Gitelman Syndrome

- Autosomal recessive
- Mutation in NCCT in distal tubule
- Milder course compared to Bartter syndrome
- Presentation
  - Adolescent/adult
  - Salt craving, polydipsia
  - Cramps, paresthesias
  - Constipation
  - Low blood pressure, fainting

Gitelman Syndrome

- Diagnosis
  - Hypokalemic metabolic alkalosis
- Hypomagnesemia
- Hypocalcicuria
- Prolonged QT interval

- Treatment
  - Magnesium supplementation
  - Monitor for diarrhea
  - Potassium supplementation
  - Spironolactone

Prolonged QT Interval in Gitelman Syndrome Patients

Differentiating Between Bartter and Gitelman Syndrome

<table>
<thead>
<tr>
<th></th>
<th>Bartter</th>
<th>Gitelman</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyhydramnios</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Failure to thrive</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Muscle weakness/fatigue</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Serum Magnesium</td>
<td>Normal</td>
<td>Low</td>
</tr>
<tr>
<td>Urinary Calcium excretion</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Urinary Sodium excretion</td>
<td>High</td>
<td>Mildly increased</td>
</tr>
</tbody>
</table>
Final Question…

Approach to Hypernatremia

Renal Collecting Tubule Water Handling

Osmolar Response to Vasopressin

Causes of Nephrogenic Diabetes Insipidus

- Congenital
  - X-linked
    - Vasopressin receptor mutation
  - AD/AR
    - Aquaporin mutation
- Acquired
  - Chronic kidney disease
  - Lithium, tetracyclines
  - Nephrocalcinosis
  - Hypokalemia
  - Sickle cell anemia
  - Sarcoidosis
  - Renal dysplasia
  - Obstructive uropathy
Diagnosis and Treatment of Nephrogenic Diabetes Insipidus

- **Diagnosis**
  - Poor feeding in first few weeks of life
  - Irritability, FTT
  - Polyuria, nocturnal enuresis
  - Mental retardation
  - Hypernatremic dehydration
  - Urine osmolality <200 despite DDAVP

- **Treatment**
  - Low salt/solute diet
  - Thiazides
  - Indomethacin

Differential Diagnosis of Polyuria/Polydipsia

<table>
<thead>
<tr>
<th></th>
<th>Primary Polydipsia</th>
<th>Central DI</th>
<th>Nephrogenic DI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Na</td>
<td>Normal/Low</td>
<td>Normal/High</td>
<td>Normal/High</td>
</tr>
<tr>
<td>Urine Osmolality</td>
<td>&lt;200</td>
<td>&lt;200</td>
<td>&lt;200</td>
</tr>
<tr>
<td>Water deprivation</td>
<td>Uosm &gt;600</td>
<td>Uosm &lt;200</td>
<td>Uosm &lt;200</td>
</tr>
<tr>
<td>DDAVP</td>
<td>Uosm &gt;600</td>
<td>Uosm &gt;600</td>
<td>Uosm &lt;200</td>
</tr>
</tbody>
</table>

Liddle’s Syndrome

- **Low-Renin hypertension**
  - Autosomal Dominant
  - Activating Mutation in ENaC
  - Hypokalemic metabolic alkalosis
  - Treatment
    - Amiloride, Triamterene
    - Low salt diet

Cystinuria

- **Due to mutations in the SLC3A1 gene**
  - Impaired cystine reabsorption results in excess cystine in the urine
  - Autosomal recessive
  - US incidence 1 in 15,000
- **Clinical phenotype**
  - Recurrent kidney stones in the young
  - Median age of onset 12-15 years
- **Treatment**
  - Hydration
  - Urinary alkalinization
  - Thiol medicaments
    - Lorenz-Depiereux et al. Nephrol Dial Transplant 2005

Renal Glucosuria

- **Mutation in the gene encoding for SGLT**
  - Most likely autosomal recessive inheritance pattern
  - Glucose detected in urine, but normal blood glucose levels
  - Clinically benign
  - Targeted by pharmaceutical companies to lower blood glucose levels in DM
    - ‘Glucuretics’

Other Selected Renal Tubular Diseases

“I’m afraid the shark got your arms and legs. It’s probably not a good time, but your brother’s here. He needs a kidney.”

Vehaskari, Pediatr Nephrol 2009

Santer, CJASN 2010

Lorenz-Depiereux et al, Am J Hum Genet 2006

Lee et al, Urology 2013

Cystinuria

Hexagonal Urinary Crystals in Cystinuria

Lee et al, Kidney Int 2008
Urinary Cystine Crystals

Due to heterozygous inactivating mutations in the calcium-sensing receptor – CASR is expressed in both the parathyroid glands and the kidneys

Leads to increased tubular reabsorption of Ca and decreased urinary Ca excretion – Results in mild hypercalcemia with low urine calcium and normal PTH levels

Diagnosis made by assessment of urine calcium excretion and CASR gene testing

Good long-term prognosis

Familial Hypocalciuric Hypercalcemia

Due to mutation in the CLCN7 gene – Results in impaired chloride transport and low-molecular weight protein endocytosis – Also may be seen with OCRL1 gene mutation

Clinical phenotype

– Hypercalciuria
– Nephrocalcinosis / nephrolithiasis
– Low-molecular weight proteinuria
– Partial Fanconi syndrome
– Progressive renal failure

End-stage renal disease in about 2/3 of affected males, 3rd-5th decade of life

• Treatment

– High fluid intake to decrease stone risk

Dent’s Disease (X-linked Recessive Nephrolithiasis)

Due to mutations in the SLC34A3 gene

Gene encodes the Na-dependent phosphate cotransporter 2c (NPT2c)

Autosomal recessive

Clinical phenotype

– Hypophosphatemia
– Rickets
– High 1,25 vitamin D
– Low PTH
– Hypercalciuria

Treatment

– Phosphate supplementation

Hereditary Hypophosphatemic Rickets With Hypercalciuria

Due to mutation in the SLCA3 gene – Gene encodes the Na-dependent phosphate cotransporter 2c (NPT2c)

Autosomal recessive

Clinical phenotype

– Hypophosphatemia
– Rickets
– High 1,25 vitamin D
– Low PTH
– Hypercalciuria

Treatment

– Phosphate supplementation

Almost over…

Key Exam Points

– Metabolic acidosis
  – Calculate the anion gap

– Hypokalemic metabolic acidosis
  – RTA, Diarrhea

– Metabolic alkalosis
  – Check urinary chloride

– Hypokalemic metabolic alkalosis
  – Bartter/Gitelman, Bulimia Nervosa, diuretic abuse, RAS

– Hypernatremia with dilute urine
  – Central/Nephrogenic Diabetes insipidus, Lithium