Acid-Base

Al Etinger

Jan 2016
Case

- CC: weakness
- HPI:
  - 27F w/ anxiety, ADD, undifferentiated autoimmune disease since 2006 (ANA+ and SS-A/SS-B +) presents with 1 day of weakness to the point where she could not get up without assistance. She felt that it was affecting her proximal muscles more than her distal muscles and lower extremity more than upper extremity. Denies laxative or diuretic use. This has never happened before. She has never experienced kidney stones.
• She had a history of arthralgia.
• ROS:
  General: +fatigue. no fevers, chills, weight change
  Chest: no shortness of breath, cough, chest pain, palpitations
  GI: no abdominal pain, diarrhea/constipation, nausea/vomiting
  GU: no dysuria, hematuria
  MSK: no joint pain, swelling
  Skin: +rash
  No history of dry mouth or dry eyes.
Other history

- **Past Surg hx:** none

- **Family hx:**
  - Father had OA and prostate cancer
  - Mother had a thyroid disease and an autoimmune disease
  - Uncle with SLE

- **Social hx:**
  - Never smoker
  - Active ETOH-social environments
  - No illicit drugs

- **Allergies**
  - Cat’s Claw-hives
Medications

• Medications:
  – plaquenil 200mg BID
  – Ativan 1 mg daily
  – Adderall 10mg daily
  – Zoloft 150mg daily
  – Microgestin daily
Physical Exam

• VS  97.6  110/63  73  18  97%

• Physical Exam:
  – General appearance: alert, appears stated age, cooperative and no distress
  – Lungs: clear to auscultation bilaterally
  – Heart: regular rate and rhythm, S1 S2
  – Abd: soft, nontender, nondistended
  – Ext: no edema. No joint swelling
  – Neuro: full ROM of all extremities. Weakness greater proximally than distally. 4/5 strength in lower extremities.
# Labs

- **CBC**
  - WBC
  - Hgb
  - Hct
  - Plt

- **BMP**
  - Na 140
  - K 2.4
  - Cl 115
  - Bicarb 17
  - BUN 17
  - Creat 0.8
  - Gluc 86

- **TSH 2.09**
- **UA (same as 07/07) pH 7.0** small protein
- **Anti SS-A >8.0**
- **Anti SS-B >8.0**
- **ANA 320**
- **dsDNA 5**
- **C3 117**
- **C4 27**
# Labs

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**VBG 09/20**  7.243/34/42/14  K 3.2

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Differential Diagnosis

- Hyperchloremic non anion gap metabolic acidosis
  - Diarrhea
  - RTA (types 1, 2, 4)

- “differential diagnosis” and discusses her rheum dx and then reviews the electrolyte picture. It says somewhere on it “non-AG metabolic acidosis” and gives the differential diagnosis of that A/B disorder.
Renal acid-base homeostasis

- Bicarbonate reabsorption
- Ammoniagenesis
- Hydrogen secretion
- Defects that lead to RTA
- Distal RTA
  - Causes
    - Genetic
    - Acquired
  - Complications
Bicarbonate in the proximal tubule

- 100% is filtered
- 80% is reabsorbed in the proximal tubule, the rest distally
  - Na-H exchanger (NHE3)
  - Carbonic acid is catalyzed by carbonic anhydrase 4 (blue circle on the luminal surface) into H2O and CO2
  - Na-bicarbonate cotransporter (NBC1) on the basolateral surface
  - Na-K ATPase on the basolateral surface is responsible for maintaining a sodium concentration gradient which allows for the excretion of H using NHE-3
- The result is that for each hydrogen ion that is secreted (on the luminal surface), there is a bicarbonate that is reabsorbed (on the basolateral surface)

Proximal (2)

- Hyperchloremic non anion gap metabolic acidosis
  - Due to a defect in proximal bicarbonate reabsorption.
  - The distal nephron is unable to compensate for the proximal part and so the urine pH is elevated due to bicarbonate loss in the urine. But the nephron does reach a steady state as the amount of bicarbonate being filtered is reduced and the distal nephrons maintain the steady state.
  - The urine pH is dependent on whether there is a bicarbonate load. If one is administered then the pH is >5.5 otherwise since there is no distal urinary acidification defect and their bicarbonate is at a steady state they can have a urine pH <5.5
  - They tend to have hypokalemia secondary to hyperaldosteronism which is caused by sodium loss with the bicarbonate.

- Complications
  - Bone disease due to metabolic acidosis and bone buffering (high in bicarbonate)
  - Hypophosphatemia due to renal wasting
  - Normal levels of urinary citrate therefore less nephrolithiasis and nephrocalcinosis—also acidified urine leads to increased solubility of Ca-P
Acid excretion

- Titratable acids such as phosphate and creatinine
- Ammonium (NH4+)
  - Product of glutamine deamination in the proximal tubule
  - Secreted via sodium-hydrogen exchanger 3 (NHE3). Which is also responsible for sodium and ammonium exchange
  - Regulated by
    - Acidosis
    - Potassium (hyperkalemia suppresses)
    - Hormones (angiotensin II and prostaglandins)

Both T, et al., Everything you need to know about distal renal tubular acidosis in autoimmune disease. Rheumatol Int. (2014) 34:” 1037-1045
Hyperkalemic (4)

- Hyperchloremic non anion gap metabolic acidosis
  - Cause is due to hypoaldosteronism, hyperkalemia or defective signaling
  - Leads to hyperkalemia which is exchanged for intracellular hydrogen. This results in an intracellular alkalosis which reduces NH4+ secretion in the proximal tubule.
  - There is also decreased hydrogen ion secretion distally because ....
  - There is no reduction in distal urinary acidification because there is reduced NH3 production and therefore less buffer for the protons that are excreted. therefore the pH can be below 5.5
  - Hyperkalemia leads to reduced ammoniogenesis (NH4+) production in the proximal tubule
  - A reduction in ammoniogenesis leads to reduced ability to excrete hydrogen ions leading to metabolic acidosis
Hydrogen in the distal tubule

- Alpha-intercalated cells
  - H-ATPase are responsible for H+ secretion
  - H/K ATPase exchanger responsible for H+ secretion and K+ reabsorption
  - CA 2 is present which produces the H+ necessary for secretion. The resulting bicarbonate is exchanged (AE1) across the basolateral membrane with Cl-
• Beta intercalated cells
  – Cl/HCO3 exchanger (pendrin)
    • Inhibited by luminal chloride deficiency
    • Stimulated by alkali load
  – Sodium driven Cl-/HCO3+ exchanger (Ndcbe)
  – CA is present within the cell.

Distal urinary acidification

• Influenced by
  – Intracellular pH (H+ concentration) and plasma PCO2
  – Distal Na+ transport and transepithelial potential difference. More Na+ reabsorption leads to a relatively negative voltage in the lumen which leads to increased H+ secretion.
  – Aldosterone-mineralocorticoids can lead to increased Na+ reabsorption and higher H+ secretion (HCO3- reabsorption)
  – Potassium depletion leads to increased H/K ATPase activity
Distal (1)

- Hyperchloremic non anion gap metabolic acidosis
  - Inability to acidify the urine (pH usually >5.5)
  - Inability to excrete acid (such as NH4+ and titratable acids such as H2PO4-)
  - Due to
    - Defect in luminal H+/K+ ATPase
    - Defect in luminal H+ ATPase on intercalated cells (collecting tubule)
  - This leads to reduced H+ secretion and reduced K+ reabsorption.
  - Leads to potassium loss in the urine and hypokalemia
- The metabolic acidosis leads to hypercalciuria, hyperphosphaturia, hypocitraturia, nephrolithiasis (Ca-P stones) and nephrocalcinosis

History lesson

• One way to diagnose distal RTA is using the ammonium chloride acidification test (an acid load)
• In a normal individual it should lower the urine pH.
• In distal RTA it will not make a difference due to the inability to excrete acid.
• Another test has been developed using lasix and fludricortisone
  – Lasix leads to increased sodium delivery to the distal tubule
  – Fludricortisone causes increased activity of the ENaC, which increases the electrochemical gradient
Distal RTA

• Problem with:
  – Transepithelial voltage defect (requires the lumen to have a negative potential difference to attract H+ (which will go down an electronegative gradient))
  – Proton gradient defect (unable to sustain large pH gradients)
  – Proton secretion defect (pump missing, cannot secrete H+)
  – Ammonium generation defect

Both T, et al., Everything you need to know about distal renal tubular acidosis in autoimmune disease. Rheumatol Int. (2014) 34:” 1037-1045
Voltage defect

- Reabsorption of Na+ via ENaC leads to a relatively negative lumen. Which creates a gradient for H+ secretion.
- ENaC is regulated by aldosterone.
- Defects can lead to hyperkalemia

Both T, et al., Everything you need to know about distal renal tubular acidosis in autoimmune disease. Rheumatol Int. (2014) 34:” 1037-1045
Proton secretion defect

- Inherited causes
  - AE1 dysfunction (AD)
  - H+ATPase (AR)
- Acquired causes
  - Include Sjogren’s
    - Mechanism is unclear
    - inhibitory autoantibodies against CA2 (1)
    - Lack of H-ATPase (case reports)
  - Medications such as topiramate and acetazolamide inhibit the activity of CA2

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Ammonium generation defect

- Low buffer state
- Primary cause is hyperkalemia
  - Reduced expression of ammoniagenic enzymes and acid transport proteins.
  - Decreased secretion of ammonia into the lumen
    - Due to competition with K at the transporter binding sites (NKCC2 and Na/K ATPase)
- This is similar to type 4 RTA

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Stones and Bones

• Chronic metabolic acidosis is associated with decreased bone density, nephrolithiasis, muscle wasting, CKD progression.
• Distal and proximal RTA are both associated with hypercalciuria and hyperphosphaturia. But distal RTA also leads to hypocitraturia. The acidosis causes citrate to be reabsorbed proximally.
• Proximal RTA is able to acidify the urine which increases the solubility calcium phosphate.
• Distal RTA is unable to and as a result it leads to nephrocalcinosis and nephrolithiasis.

Distal RTA Treatment

• Alkali repletion (Sodium bicarbonate or Sodium Citrate) to buffer the protons that are not excreted.
• If hypokalemia persists despite correction of the metabolic acidosis, then Potassium Citrate can be used
• K-citrate can lead to hyperkalemia
The End