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**Approach to Pediatric Hypocalcemia**

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Hi my name is Madeline Parker, I am a pediatrics resident at the University of Saskatchewan. This podcast was developed with Dr. Munier Nour, a pediatric endocrinologist at Jim Pattison Children’s Hospital in Saskatoon, Saskatchewan. This podcast will discuss hypocalcemia and will be followed by a second podcast on hypercalcemia.

By the end of this podcast, listeners will be able to:

1. Describe the roles of parathyroid hormone and Vitamin D in calcium homeostasis
2. List clinical features of symptomatic hypocalcemia
3. Identify initial investigations required to determine the etiology of hypocalcemia in children
4. Outline the initial the management of symptomatic hypocalcemia

**Let’s start with a clinical case.**

While on your Pediatrics rotation, you are asked to evaluate an 8-year-old girl for obesity. She has been treated for congenital hypothyroidism since birth and is diagnosed with a mild intellectual disability. Prior to coming in today, she had routine lab work. While the patient is in the clinic waiting room, the lab calls to report a critically low calcium level of 1.65 mmol/L.

**Before addressing this patient’s hypocalcemia, let’s first take a moment to talk about how the body regulates calcium.**

The skeleton is the body’s primary calcium reservoir, with 99% of the total body calcium stored in bone as hydroxyapatite crystal. The remaining 1% exists in the extracellular fluid, of which 50% in the free ionized form, 40% bound to protein—primarily albumin—and 10% complexed with anions, such as citrate1. The free ionized form is biologically active and is tightly regulated, playing an important role in enzymatic activity, blood coagulation, and neuromuscular excitability2.

To avoid disruptions of these vital functions, disturbances in ionized calcium are quickly corrected through the coordinated action of parathyroid hormone, vitamin D, and the calcium-sensing receptor, a G-protein coupled receptor expressed in various tissues, including the parathyroid gland and kidney3.

**So how does this system regulate serum calcium?**

The calcium-sensing receptor detects changes in ionized calcium and corrects this by altering parathyroid hormone release and calcium reabsorption at the nephron. When ionized calcium is low, calcium-sensing receptors stimulate parathyroid hormone release and increase calcium reabsorption at the renal tubules. In the setting of hypercalcemia, the opposite occurs3.

This brings us to the role of parathyroid hormone, which increases serum calcium through its direct action on bone and the kidney and indirect action on the gastrointestinal system via activated Vitamin D. The sustained effect of parathyroid hormone on bone causes a release of calcium and phosphate into the blood. While this increases serum calcium, the net effect is a reduction in serum phosphate, which we will explore shortly.

At the kidneys, parathyroid hormone has two major effects. First, it stimulates the 1-alpha hydroxylase enzyme which converts inactive 25 Hydroxy vitamin D into active 1,25 Dihydroxy vitamin D which then acts on the intestinal mucosa, increasing the active transport of both calcium and phosphate. Second, parathyroid hormone causes calcium reabsorption in the distal convoluted tubule and indirectly increases phosphate excretion via a hormone called FGF23. The renal phosphate excretion generally exceeds intestinal absorption and bone resorption, thus causing a net reduction in serum phosphate levels. It is important to note hyperphosphatemia or phosphate loads also serve as triggers for parathyroid hormone release5.

**So what’s the big picture?**

To summarize, parathyroid hormone release is triggered by hypocalcemia or an increase in serum phosphate. In the setting of hypocalcemia, the secretion of parathyroid hormone is triggered by the calcium sensing receptor. Parathyroid hormone acts directly on bone and in the kidneys and indirectly via Vitamin D on the intestines. Ultimately, it increases serum calcium, activates vitamin D, and reduces serum phosphate5.

**So let’s go back to our patient with hypocalcemia.**

As you recall, your patient with a history of congenital hypothyroidism is now found to have hypocalcemia. You take a moment to review the rest of her lab work before proceeding to see the patient.

Initial investigations are significant for hypocalcemia, with a calcium of 1.65 mmol/L, and hyperphosphatemia, with a phosphate of 2.89 mmol/L. The CBC and remainder of her electrolytes are normal. TSH and free T4 are within the normal range.

**Your preceptor asks you what signs and symptoms you might anticipate, and how will you focus your history and physical, given this patient’s hypocalcemia.**

In hypocalcemic states, there is increased neuromuscular excitability due to mechanisms beyond the scope of this podcast. In young and non-verbal children, this manifests as muscle spasms, feeding difficulties, or jitteriness. Older children may complain of muscle spasms and cramps, paresthesia, or numbness. Life-threatening symptoms can affect all ages and include: seizures, arrythmias—particularly QT prolongation—and laryngospasm, which may present with dyspnea or stridor1,6. The symptoms of hypocalcemia are related to the severity and chronicity, with more rapid and acute reductions in calcium presenting in a more symptomatic fashion5. History should be directed at establishing whether the patient is symptomatic from their hypocalcemia.

On physical examination, start by assessing vitals as well as airway, breathing, and circulation due to the possibility for severe cardiorespiratory symptoms. Then proceed with a complete physical examination and check for tetany using Chvostek and Trousseau’s signs. Chvostek’s sign is performed by tapping the facial nerve just anterior to the ear and watching for contraction of the ipsilateral facial muscles. Trousseau’s sign is examined for by inflating a blood pressure cuff to above systolic blood pressure for 3 minutes and watching for carpal spasm1.

**Going back to our case**…

The patient has no symptoms of hypocalcemia and her vitals are stable. BMI is above the 95th percentile for age and sex. Chvostek’s and Trousseau’s signs are negative. The remainder of the examination is unremarkable, with the exception of brachydactyly of the 4th fingers and toes. X-Rays of the hands and feet reveal this is due to short 4th metacarpals and metatarsals. To rule out QT prolongation you also order an ECG, which demonstrates sinus rhythm and a normal corrected QT interval.

**Given this information, what are some important considerations before proceeding with any further investigations?**

First, it is important to exclude shortfalls of laboratory testing. As previously mentioned, the serum calcium available in circulation is found either in its biologically active ionized form or bound to albumin and other proteins. As a result, reductions in serum albumin will result in reductions in the measured total calcium concentration. However, as calcium homeostasis mechanisms remain intact, patients with low total calcium due to hypoalbuminemia will have normal ionized calcium concentrations, thus remain asymptomatic. This lab aberration is given the term pseudo-hypocalcemia and can be confirmed easily with a calcium correction formula readily available online.

In contrast, acute changes in acid-base status can alter ionized calcium levels, resulting in true hypo or hypercalcemia. Because protons compete with ionized calcium to bind albumin, acidosis and alkalosis can cause hyper and hypocalcemia, respectively. While these shifts may potentially become symptomatic, they generally occur with acute changes to acid/base status and do not persist in the chronic state, provided homeostatic mechanisms are intact1,5.

If calcium is abnormal despite correcting for albumin and identifying and treating any underlying acid/base disturbances, evaluation for the etiology of hypocalcemia is required.

**Going back to our case. Our patient’s albumin and pH are within normal limits. As a result, it is important to consider other diagnoses.**

To do so, we need to determine how the components of calcium metabolism are behaving. Initial investigations should therefore include PTH, vitamin D, phosphate, urinary calcium, and a spot urine Ca:Cr ratio5. To narrow our differential, we should first determine if PTH is responding appropriately. In the setting of hypocalcemia, PTH should increase to normalize serum calcium. Thus, a low or even a normal PTH concentration is inappropriate and indicates likely hypoparathyroidism. Hypoparathyroidism in infants and children may be congenital or acquired.

**Let’s start by discussing congenital causes of hypoparathyroidism.**

Congenital hypoparathyroidism is caused by disorders of parathyroid gland development or function.

DiGeorge syndrome is an example of a disorder impacting parathyroid gland development. Clinical features include hypocalcemia from parathyroid aplasia or hypoplasia, cardiac defects, renal anomalies, immune dysfunction and craniofacial abnormalities3.

A complete discussion of the inherited causes of hypocalcemia is beyond the scope of this podcast. However, it is important to note inherited hypoparathyroidism displays numerous modes of transmission and can also occur as a feature of other genetic conditions, such as mitochondrial disorders3.

**Before returning to our case, let’s move on to discuss the causes of acquired hypoparathyroidism.**

There are several distinct causes of acquired hypoparathyroidism:

1. First, neonates born to women with hyperparathyroidism during pregnancy can present with hypocalcemia in the first weeks to month of life due to transient suppression of fetal PTH release. This resolves as their own parathyroid gland function is slowly restored3,7.
2. Second, hypomagnesemia prevents secretion of parathyroid hormone, resulting in a transient acquired hypoPTH9.
3. Third, hypoparathyroidism can result from parathyroid destruction due to autoimmune disorders8, glandular infiltration3, radiation therapy, or neck surgery—the classic example being post-thyroidectomy3.

Both congenital and acquired hypoparathyroidism are characterized by hypocalcemia with hyperphosphatemia, and decreased active vitamin D. Inactive 25-OH vitamin D, which is commonly used to measure sufficiency, will remain unchanged as its synthesis does not require PTH8. This point will be important to remember when we talk about treatment later on.

**For now, let’s return to our case. PTH is appropriately elevated at 62 pmol/L, indicating that our patient does not have hypoparathyroidism as the cause for her hypocalcemia.**

**What is the approach to hypocalcemia when PTH is elevated?**

In the context of hypocalcemia, elevated PTH indicates the parathyroid glands are intact and hypocalcemia is a result of aberrations elsewhere in calcium homeostasis. Causes of hypocalcemia with elevated PTH can be subdivided into whether they are vitamin D related or not. The causes of vitamin D-related hypocalcemia include vitamin D deficiency and disorders of vitamin D metabolism5.

**Before discussing the causes of vitamin D deficiency, let’s briefly review vitamin D synthesis.**

Vitamin D precursors are derived from sunlight-dependent chemical reactions in the skin and dietary sources. After intestinal absorption, they are transported to the liver, where they undergo hydroxylation into inactive 25(OH) vitamin D, in a PTH independent process. Under the influence of PTH, inactive vitamin D is converted into active 1,25(OH)2 vitamin D by the 1-alpha hydroxylase enzyme in the kidneys. Active vitamin D then increases intestinal absorption of calcium and phosphate4,5.

Thus, the expected biochemical profile of hypocalcemia secondary to vitamin D deficiency is increased PTH with reduced 25-OH vitamin D. Calcium and phosphate may be decreased in severe cases, leading to rickets.

**Given that a functioning GI tract, liver, kidneys, and exposure to sunlight are needed for the synthesis of vitamin D, who is at greatest risk for deficiency?**

Children who live at higher latitudes and those with darker skin pigmentation, malnourishment, liver failure, biliary atresia, inflammatory bowel disease, or cystic fibrosis are at increased risk for vitamin D deficiency due to decreased synthesis or absorption of necessary precursors. Infants breastfed exclusively past 6 months are also at risk, as maternally-derived stores begin to wane at 6 months and breastmilk is a poor source of vitamin D4. Depletion of vitamin D occurs earlier in infants with inadequate stores due to prematurity or maternal vitamin D deficiency10. Lastly, medications can interfere with hepatic vitamin D metabolism, including anticonvulsants, antiretrovirals, and antifungals4.

**We will now move on to briefly discuss disorders of vitamin D metabolism.**

Vitamin D related hypocalcemia is rarely caused by mutations in the genes encoding the 1-alpha hydroxylase enzyme or vitamin D receptor, thereby preventing the synthesis of and response to active vitamin D, respectively. These disorders are extremely rare and should be suspected when vitamin D deficiency is resistant to standard treatment or when 25(OH) vitamin D levels are normal, but the biochemical profile is otherwise consistent with vitamin D deficiency 4,5.

**Returning to our case. The remainder of our patient’s bloodwork has returned and 25(OH) Vitamin D is normal at greater than 75 nmol/L. How should we approach hypocalcemia when vitamin D is normal and PTH is appropriately elevated?**

As previously mentioned, when PTH is elevated in the setting of hypocalcemia, it is important to look for abnormalities elsewhere in calcium homeostasis. Given that our patient’s vitamin D is normal, this brings us to the non-vitamin D related causes of hypocalcemia, which include hyperphosphatemia, kidney disease, and PTH resistance.

**Let’s start by discussing hypocalcemia due to hyperphosphatemia and kidney disease, as they are related.**

Hyperphosphatemia causes hypocalcemia by precipitating with calcium. To normalize both phosphate and calcium, PTH increases. There are three major causes of hyperphosphatemia:

1. First, an excessive phosphate load can cause hyperphosphatemia. This is unlikely to occur due to the ingestion of phosphate-rich foods or supplements in patients with normal kidney function but can occur from the excessive use of phosphate-containing enemas.
2. Second, massive release of intracellular phosphate from tumor lysis or rhabdomyolysis.
3. Third, decreased excretion of phosphate, due to acute renal failure or chronic kidney disease. In patients with renal disease, hypocalcemia is multifactorial and typically only occurs in advanced disease. It is triggered by both hyperphosphatemia and decreased vitamin D activation secondary to impaired 1-alpha hydroxylase activity. This is the result of a reduction in renal mass and hyperphosphatemia, which displays negative feedback on active vitamin D synthesis11.

Regardless of the cause, the biochemical profile of patients with hyperphosphatemia will reveal increased PTH, hypocalcemia, and normal 25-OH vitamin D levels. In patients with chronic kidney disease, active vitamin D will be decreased5.

**Before returning to our case, there are several other causes of non-vitamin D related hypocalcemia that are worth considering.**

For example, hypocalcemia can occur in severely ill patients with sepsis, burns, or pancreatitis. It can also occur as a medication side effect from the administration of bisphosphonates, denosumab, calcimimetics, and certain chemotherapy agents. Lastly, citrate in large volume blood transfusions can complex with calcium, causing hypocalcemia5.

**Going back to our case. Our patient’s phosphate is elevated at 2.9 mmol/L. Creatinine and urea are normal, indicating normal renal function. There are no features on history, physical or in the remainder of her laboratory results concerning for cell breakdown, excess enemas, or drug-induced hypocalcemia. Given this information, what is the most likely cause of our patient’s hypocalcemia?**

In the absence of vitamin D deficiency or any obvious causes of hyperphosphatemia, hypocalcemia with hyperphosphatemia and elevated PTH is suggestive of PTH resistance, which is also referred to as pseudohypoparathyroidism, or PHP. There are numerous subtypes of PHP, however, the most common is PHP1a, also known as Albright’s hereditary osteodystrophy. Affected individuals can have resistance to multiple hormones which exert their effects through G-protein coupled receptors, due to a mutation in the *GNAS1* gene, which encodes a protein necessary for post-receptor signaling.

The patient in our case displays many of the characteristic features of Albright’s, which include intellectual disability, short stature, obesity, brachydactyly and a round face. Due to widespread dysfunction of G-protein coupled receptors, patients may also display resistance to gonadotropins and thyroid stimulating hormone, resulting in hypogonadism and hypothyroidism, respectively3.

In Albright’s, the expected biochemical profile is hypocalcemia, hyperphosphatemia, and decreased active vitamin D due to an inability to respond to PTH, leading to an elevated serum PTH concentration. 25-OH vitamin D should be intact. The diagnosis can be confirmed genetically5.

**Now that we’ve determined our patient’s diagnosis, it’s important to consider the treatment of hypocalcemia.**

**As previously discussed, the symptoms of hypocalcemia can range from asymptomatic—as in our case—to life threatening. Let’s start by discussing the initial management of acute symptomatic hypocalcemia.**

An initial bolus of IV calcium is recommended in patients with severe or symptomatic hypocalcemia, particularly tetany, seizures, carpopedal spasm, laryngospasm and QT prolongation13. Before treatment, patients should be placed on continuous cardiac monitoring due to the possibility for arrhythmias from calcium administration. Although no universally adopted protocol exists, a 10-20 minute IV infusion of 2 mL/kg of 10% Ca gluconate or 0.7 mL/kg of Ca chloride is generally recommended. Additional boluses can be given if symptoms persist1. Serum magnesium should be assessed to ensure treatment is successful as low Mg can impede treatment effect.

After calcium bolus administration, ongoing calcium infusion or intermittent IV doses may be needed to prevent recurrence13.

**We will now move on to an overview of the long-term management of hypocalcemia.**

Treatment with oral therapy should be started after the symptoms of hypocalcemia are controlled1. It is also the preferred initial treatment in asymptomatic patients and in those with only mild symptoms, such as paresthesias. The specific oral treatment depends on the underlying cause of hypocalcemia. In hypoparathyroidism and pseudohypoparathyroidism, activated vitamin D and calcium supplements are required. In hypocalcemia due to vitamin D deficiency, supplementation with inactive vitamin D is generally sufficient. However, active vitamin D may be required in rare cases, such as in liver disease or a disorder of vitamin D metabolism13. In chronic renal failure, phosphate binders and activated vitamin D are used to minimize secondary PTH release and protect bone health12.

**This brings us to our patient’s treatment.**

Because our patients with Albright’s is unresponsive to PTH, she requires activated vitamin D and calcium supplements. She also needs regular investigations to ensure serum calcium is maintained in the low normal range and ensure urinary calcium excretion is not elevated. Further, she requires ultrasound assessments for the possible development of nephrocalcinosis due to therapy.

**We have now discussed hypocalcemia from initial presentation to management.** To summarize, patients with hypocalcemia can present without symptoms or with symptoms of neuromuscular excitability. Life-threatening manifestations including laryngospasm, seizure, and QT prolongation can occur and require immediate treatment.

To determine the underlying cause of hypocalcemia, it is important to first consider if PTH is responding appropriately. If PTH is inappropriately low, the diagnosis is hypoparathyroidism. If PTH is appropriately high, the diagnosis is either vitamin D related or due to hyperphosphatemia, kidney disease, or PTH resistance. In acutely symptomatic patients, treatment includes administration of an IV calcium bolus followed by ongoing calcium therapy as required. Long term therapy for hypocalcemia depends on the underlying cause.

**Let’s review our learning objectives. We hope that after listening to this podcast, you will now be able to:**

1. Describe the roles of parathyroid hormone in Vitamin D and calcium homeostasis
2. List clinical features of symptomatic hypocalcemia
3. Identify initial investigations required to determine the etiology of hypocalcemia in children
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**Thank you for listening! We hope you join us for our podcast on pediatric hypercalcemia!**

**References**

1. Zhou P, Markowitz M. Hypocalcemia in Infants and Children. *Pediatrics in Review* 30(5) 190-192. May 2009.
2. Jain A, Agarwal R, Sankar MJ, Deorari A, Paul VK. Hypocalcemia in the Newborn. Indian Journal of Pediatrics. 77: 1123-1128. August 2010.
3. Kliegman RM, St Geme III JW, Blum NJ, Tasker RC, Shah SS, Wilson KM. Nelson Textbook of Pediatrics. 21st Edition. Philadelphia, PA. Elsevier; 2020.
4. Ariganjoye R. Pediatric Hypovitaminosis D: Molecular Perspectives and Clinical Implications. *Global Pediatric Health*. 4: 1-7. November 2016.
5. Nour M. Calcium Physiology & Clinical Calcium [Lectures]. Saskatoon: University of Saskatchewan, College of Medicine; 2018 [cited 2020 Nov 18]. Available upon request.
6. Pediatric hypocalcemia: making the diagnosis. *Canadian Medical Association Journal.* 177 (12); 1495-97.
7. Jain A, Agarwal R, Sankar MJ, Deorari A, Paul VK. Hypocalcemia in the Newborn. *Indian Journal of Pediatrics.* 77: 1123-1128. August 2010.
8. Husebye ES, Perheentupa J, Rautemaa R, Kämpe O. Clinical manifestations and management of patients with autoimmune polyendocrine syndrome type I. *Journal of Internal Medicine.* 265: 514-529. 2009.
9. De Sanctis V, Soliman A, Fiscina B. Hypoparathyroidism: from diagnosis to treatment. *Current Opinion in Endocrinology, Diabetes and Obesity.* 19 (6) 435-442. December 2012.
10. Godel JC. Vitamin D supplementation: Recommendations for Canadian mothers and infants. *Paediatr Child Health.* 12(7):583-9. October 2007.
11. Stubbs JR, Yu ASL. Overview of the causes and treatment of hyperphosphatemia. *UpToDate.* Last Updated: June 2020. Available from: https://www.uptodate.com/contents/overview-of-the-causes-and-treatment-of-hyperphosphatemia?search=hyperphosphatemia&source=search\_result&selectedTitle=1~150&usage\_type=default&display\_rank=1
12. Srivastava T, Warady BA. Pediatric chronic kidney disease-mineral and bone disorders (CKD-MBD). *UpToDate.* Last updated: June 2020. Accessed from: <https://www.uptodate.com/contents/pediatric-chronic-kidney-disease-mineral-and-bone-disorder-ckd-mbd?search=renal%20osteodystrophy&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1>
13. Goltzman D, Rosen CJ. Treatment of hypocalcemia. *UpToDate.* Last Updated July 2020. Available from: https://www.uptodate.com/contents/treatment-of-hypocalcemia?search=Hypocalcemia%20treatment&source=search\_result&selectedTitle=1~150&usage\_type=default&display\_rank=1