

SPEAKER:

So why don't we review a little bit of anatomy first, so we know what we're all talking about. The parathyroids are tiny little glands that are located next to the thyroid gland, hence the Latin kind of juxtaposition of the names. Typically, you're going to have four, although some people have five, six. It's even been reported to have 12 in some folks.

But mostly four. Two on the right side of the neck, two on the left side of the neck, and the anterior portion, just in front of the-- or around the trachea, if you will. Normal glands are about the size of a grain of rice. And when we're operating around this area, the parathyroids are often really challenging to see in juxtaposition to all the normal fat structures and things like that. Very easy to miss or accidentally damage or remove.

Their locations are also interesting. I just told you that they're typically located right here in the neck. But depending on how the embryological migration of these little glands do when you're a tiny little multicellular thing growing in the womb, it can be located as high up as high up in the cervical spine and in the back of the neck, and all the way down to near the heart and the mediastinum. So they can be located in weird places, and that makes our job pretty interesting when we do see those cases.

So the primary function of the parathyroid. They punch far above their weight class. They are the most important glands that control calcium homeostasis in the body. Some people may have heard of calcitonin. That's another hormone. But that plays a much more minor role.

So parathyroid hormone, or PTH, is secreted by the parathyroid. And the pattern and the amount that they're secreted is incredibly tightly controlled, based on the level of serum calcium that's in your bloodstream, so the serum concentration of calcium.

So in response to a dip in the serum calcium, PTH is secreted. So you have the seesawing effect. And then what happens when PTH is made more available in the body, it exerts effects on many different organ systems. So for the bones, it starts to break down bone-- osteoplastic activity-- releases calcium into the bloodstream.

When it comes to the kidneys, it tries to stop the filtering of calcium through the urine, keep the calcium inside the serum. Another thing that it does indirectly is it increases the production of activated vitamin D, which then causes more GI absorption of calcium from your diet. So all of those things will help get the calcium to be higher.

And once the calcium is depleted, there is this negative feedback loop that tells the parathyroid to stop working so hard. So it's very, very nicely controlled. It's the perfect system, except when it goes wrong.

So primary hyperparathyroidism is when one or more of these glands happens to become an autonomous bully, so to speak. It gets bigger. It does not respond to the negative feedback loop and just pumps out PTH, regardless of what the calcium levels are.

So you can imagine that upsets the balance of things. So it just constantly is starting to tell the bones to release calcium, break down bone, get the bones thinner. You can also see that the calcium just gets higher and higher in the blood, leading to hypercalcemia. And that can overwhelm the kidneys and start having calcium spillage through the kidneys. And I'll go into how that can be bad. And then a number of other things that we'll talk about.

So what causes primary hyperparathyroidism from a pathology perspective? I just said most of the time, it's because one out of the four tumors becomes a benign, hyperfunctioning adenoma, so just an enlarged, juicy parathyroid. I told you that it's usually the size of a grain of rice. Adenomas can wind up looking more like, let's say, a kidney bean, something like that, or maybe a little bit larger.

That's the vast majority. Sometimes you could have what's called multi-gland disease. But that's a little bit less common.

A little sliver here on this pie chart for what causes hyperparathyroidism. The green sliver is for parathyroid cancer. We almost never see parathyroid cancer. But when it happens, it's pretty obvious.

The calcium levels go up to really dangerous levels. The patients are coming with mental status changes, potentially going into comas. EKG changes. They're severely

dehydrated. Their organs may be shutting down if you don't catch them in time. thankfully, it's a very rare thing.

So what are the general symptoms? Now, thankfully, due to modern medicine, we have routine lab tests, so you can just almost order willy nilly, depending on what you are looking for. If you order a chem panel, usually a calcium is going to be a part of it, even though that's not something you're necessarily looking for. So people are getting caught with milder and milder forms of disease, as opposed to how it was before these lab tests were so commonplace, when those severe symptoms, like what I told you for parathyroid cancer, would occur for even benign disease.

So what is the usual symptom profile? There is a mnemonic that people all learn in school. Hypercalcemia causes things with stones, bones, groans, and psychic overtones. So if you think of all those things, you go down that list-- bones. Bone thinning leads to bone loss. Osteoporosis can increase the risk of fragility type fractures.

Stones means kidney stones. We just talked about how the kidneys are taking up a lot of load with all that calcium that's spilling through. Sometimes that calcium is going to precipitate and form stones. That can also cause chronic kidney damage in the future, if it's just constantly being overworked.

Groans are GI symptoms. Now, it used to be that you could see pancreatitis, peptic ulcer disease, from hypercalcemia. Now, with milder levels, the most common symptoms that people have is constipation. It's admittedly non-specific. But some people will report that their constipation is vastly improved after having their hyperparathyroidism treated.

Psychic overtones. So this is an often underrepresented symptom profile, even though it's pretty important. These are cognitive, or neuropsychiatric, defects that can occur as a result of elevated calcium. These can take the form of either memory loss, concentration deficits, insomnia, depression, other mood changes, you name it. The feeling of badness has been reported on many fronts from parathyroid disease.

So as it turns out-- green slide here-- gender does play an important role in how

patients would typically present with this disease. So the University of Wisconsin, back in 2012, reviewed their latest 1,300 patients. They're a major center for endocrine surgery.

What they had found when they reviewed all those charts and the way that their patients presented were that women were much more likely to present in a unique profile at a later age compared to men, perhaps because they just didn't want to bother. Maybe there were some other things that they thought that their symptoms were due to otherwise. They were more likely to present with symptoms.

There is a form of hyperparathyroidism that doesn't come with symptoms per se. It's just an elevated calcium. But the women were more likely to come with symptoms, either kidney stones or what have you. And they were also more likely to present with osteoporosis, much more important with women as opposed to men. Men were more likely asymptomatic. But when they were to come to the clinic with symptoms, it was because of kidney stones.

So as it turns out, primary hyperparathyroidism is a fairly common endocrine disorder. The other thing is it's about a three to one female to male ratio in terms of how it presents. It's most commonly diagnosed in the 50s to 60s, although I've seen patients as young as in their 20s. My personal record is a lady who is 93 or 94 years old with that diagnosis. It's also important to emphasize that chronic hypercalcemia, if one sees it, can be attributed to primary hyperparathyroidism 90% of the time.

So on that list of differential diagnoses, which is this, there's a lot of things that can cause elevated serum calcium. 90% of the time in people who otherwise don't have any major reasons, like cancer or something, to have elevated calcium levels, it's because of primary hyperpara. So it's completely reasonable and/or if not encouraged for folks to be checking a PTH level if they happen to find even a mildly elevated serum calcium.

So the interesting thing is, even though primary hyperpara is fairly common as far as we know, we're still probably underestimating its true incidence. And that's because of under diagnosis, most likely. This pie chart is from a study that the Cleveland Clinic had done. They published it a few years ago.

They reviewed their latest three million electronic medical records of patients. And they had found the subset of patients that had hypercalcemia. So ignore the pie on the left. That's in the folks that they had determined, based on their history, that they were unlikely to have primary hyperparathyroidism.

On the right side are the folks that likely because they had kidney stones or they had osteoporosis, they likely had primary hyperpara. And yet almost 50% of the time, a PTH was never checked for the entirety of their care. And this was in a closed, advanced health care system, Cleveland Clinic, also happens to be one of the world's major sites for endocrinology and endocrine surgery. So you can imagine even with that level of outreach, people are still not actually catching this often enough.

Some risk factors for primary hyperpara-- female gender. I already mentioned that. Other things include significant radiation exposure to the head and neck region. We're not talking about dental X-rays or CT scans. We're talking people who have had radiation treatments. There have been a lot of studies back in the day with nuclear disasters and their association with both thyroid and parathyroid disease.

A family history. Sometimes some familial syndromes can predispose to primary hyperparathyroidism. And lastly, even though it's not as common these days, people who have been on long term lithium for bipolar disorder. Something about the lithium is a direct stimulator of parathyroid cells.

So you can imagine that's sort of a difficult population to treat, because there's a reason why people are on long term lithium with all of these other medications available. They probably need it. And yet you have to take them off of it and then do all these tests and try to treat them.

So why don't we go a little bit into why do we think primary hyperpara is more common in women than in men. The answer is not clear. And I'm just going to share some theories that have been bandied about a little bit.

In 2012, this group from Sweden had done some basic science experiments on parathyroid tissue coming from men and women. And they had actually found that there was a high proportion of estrogen receptor that was produced in parathyroid cells, particularly in women.

Now, does that necessarily prove that because estrogen is more a female hormone that that's going to directly correlate to a rise in parathyroid disease? Not necessarily. But the clinical evidence is starting to-- a little bit of anecdotal evidence is starting to develop.

This is a study that tied the incidence of breast cancer in Italy to a higher incidence of primary hyperparathyroidism. So you can imagine, breast cancer, obviously estrogen and estrogen receptor has a lot to do with the pathogenesis of breast cancer. Could that also be colocalizing with the development of benign parathyroid disease? Perhaps. But again, these are still theories no one has been able to completely prove one way or the other.