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### Therapeutic Options for ADH1 and Hypoparathyroidism

#### Announcer:

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#### Dr. Schweiger:

Hello, everybody. Thank you for joining us today. My name is Michelle Schweiger, Pediatric Endocrinology here at Cedars Sinai. Our topic for today is therapeutic options for ADH1 and hypoparathyroidism. And it's with great pleasure to introduce Dr. Michael Levine from Children's Hospital Philadelphia.

#### Dr. Levine:

Good day. How are you, Michelle?

#### Dr. Schweiger:

Good. Thank you.

#### Dr. Levine:

I look forward to our conversation.

#### Dr. Schweiger:

Thank you. I wanted to start by asking, Dr. Levine, since hypoparathyroidism is the only endocrine deficiency state that does not have an approved form of hormone replacement therapy, can you please tell us about conventional therapy of hypoparathyroidism? And how this approach can be used to treat patients with ADH1?

#### Dr. Levine:

Well, you touch on a sore point here that reminds us that hypoparathyroidism is the endocrine stepchild, in that there isn't a hormonal form of replacement therapy for hypoparathyroidism. We don't have the ability right now to prescribe parathyroid hormone to patients who have hypoparathyroidism. And this is very different from the situation with all other endocrine deficiency states. So, this is a tough one for us.

And conventional therapy, which is the current therapy, consists of using an active form of vitamin D. So, either 1 alpha or calcitriol plus oral calcium supplements. And it's important to note that the oral calcium supplements really serve two important roles. One, they allow the patient to have a consistent intake of calcium that doesn't vary by day-to-day differences in dietary intake of foods that have calcium. So, that's important, you're providing a consistent source of enteral calcium. But perhaps even more importantly, the oral calcium supplements provide a means of controlling hyperphosphatemia, which is the other part of hypoparathyroidism. And the oral calcium supplements will bind phosphate in the GI tract and reduce serum phosphorus levels.

And it's important to remember that managing hypoparathyroidism really is managing hyperphosphatemia. So, whenever a physician is managing a patient with hypoparathyroidism, and checking serum calcium levels, they should also check the serum phosphate level.

You can't manage hypopara if you don't know what the serum phosphate level is.

Now in terms of the utility of conventional therapy, about 80% of patients with hypoparathyroidism due to some damage or removal or genetic defect or the parathyroid gland other than ADH1, will do reasonably well on conventional therapy. But about 20% of patients will fail to meet either biochemical targets or they'll continue to have signs of neuromuscular or cognitive difficulty. And for these patients, replacement therapy with parathyroid hormone really is important.

The problem is when we get to ADH1, we're not only missing PTH, but we've got this activated calcium-sensing receptor to deal with. And in studies in which patients with ADH1 were given PTH replacement, either PTH 1-34 or recombinant human PTH 1-84, there was normalization of serum calcium and serum phosphorus, some improvement in urinary calcium levels, but not normalization of urinary calcium excretion. So, PTH replacement therapy can be wonderful for patients with post-surgical hypoparathyroidism and other genetic causes of hypoparathyroidism. But PTH replacement therapy really isn't the right approach for patients who have ADH1 and do have an activated calcium-sensing receptor.

**Dr. Schweiger:**

Are there any pitfalls of conventional therapy in ADH1?

**Dr. Levine:**

Well, for all forms of hypoparathyroidism, we target a serum calcium level that will be high enough to relieve neuromuscular symptoms, but not so high as the cause hypercalciuria. So, there's a balance that we have to strike; a serum calcium level that's typically in the low-normal range that will relieve neuromuscular symptoms but avoid hypercalciuria. This whole balance is shifted in a completely untenable way in patients who have ADH1. At any serum calcium level, a patient with ADH1 will have a far greater urinary calcium excretion than a patient with other forms of hypoparathyroidism.

So, we have to really pay close attention to the urinary calcium excretion in patients with ADH1. We have to look at urinary calcium frequently either by 24-hour urines or random urine for calcium/creatinine ratio, again, using age-dependent normal ranges for the calcium/creatinine ratio, as well as for the 24-hour urine calcium. And we also have to use imaging studies, such as ultrasound, to monitor the kidneys to see whether nephrocalcinosis or even renal stones are forming.

All this becomes far more important to do in patients with ADH1 compared to patients who have other forms of hypoparathyroidism, because they have this much higher fractional excretion of calcium, and will have very high urinary calcium levels, and are far more likely to develop renal stones and progressive renal insufficiency than other patients with other forms of hypoparathyroidism.

**Dr. Schweiger:**

Given that hypercalcemia is such a concerning feature of ADH1, how do you go about monitoring and managing this complication? For instance, do thiazides work in ADH1?

**Dr. Levine:**

So, there hasn't been a lot of research into the utility of thiazides and thiazide-type diuretics in patients with ADH1. There are some case reports that suggest that patients with ADH1 will respond to thiazides. But in my experience, they don't respond to thiazides as well as patients with other forms of hypoparathyroidism. And I think this is because there is not only an increase in urinary calcium excretion, but also an increase in urinary sodium excretion. And the increase in urinary sodium excretion can overcome, I think, the pharmacological action of thiazides. And the thing to remember when you're using a thiazide in any patient with hypoparathyroidism is that the thiazide will work best if the patient is also on a low sodium diet; a high salt intake can overcome any potential benefits of a thiazide in reducing the urinary excretion of calcium.

**Dr. Schweiger:**

As you mentioned previously, many patients with ADH1 will also manifest a form of Bartter syndrome. Is supplementation with magnesium and potassium necessary in these patients?

**Dr. Levine:**

This is a very tough thing to treat. Many of these patients will require very large amounts of magnesium, and it's a struggle to keep their serum magnesium level over 1.0 mg/dL. Many of them will also require potassium; and here, we use a combination of potassium chloride and potassium citrate. But the magnesium is a problem, because if you give too much magnesium, patients will often develop loose stools or diarrhea. And I think it's, in many cases, the low magnesium that amplifies the symptoms, the neuromuscular symptoms of hypocalcemia in patients with ADH1.

**Dr. Schweiger:**

Thank you, everyone, for joining us today. I want to say thank you from here in California.

**Dr. Levine:**

And take care from Philadelphia.

**Announcer:**

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