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Increasing ADH1 Awareness: A Hidden Cause of Hypoparathyroidism

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Dr. Schweiger:
Hello, everyone. Thank you for joining us today. My name is Michelle Schweiger. I'm the Director of Pediatric Endocrinology here at Cedars Sinai Medical Center. It's with great pleasure to be speaking on the topic of ADH1 in hypoparathyroidism. And Dr. Michael Levine from the Children's Hospital of Philadelphia will be joining me today.

Dr. Levine, autosomal dominant hypocalcemia type 1 is recognized as a cause of hypocalcemia, which could often be mild and asymptomatic, and sometimes severe and clinically significant. How do you go about evaluating a patient who presents with symptoms of hypocalcemia, or who is discovered to have hypocalcemia on routine blood tests?

Dr. Levine:
Well, the first thing we want to do is make sure that we're not dealing with artefactual hypocalcemia, so we'll check in albumin level and do an albumin adjusted calcium level. And then the second approach really consists of looking at hypocalcemia as existing in two buckets. One is the vitamin D bucket, and the other is the parathyroid hormone bucket. And in the vitamin D bucket, we're looking at patients who have deficiency of vitamin D, and those patients will develop secondary hyperparathyroidism, their serum of phosphate levels will be low. On the other hand, if there's a problem in parathyroid hormone production or responsiveness, then we'll see an elevation in the serum phosphorus level. So, looking at the calcium first, and then the serum phosphorus is really very important.

And I would point out that the interpretation of a serum phosphate level has to take into account the patient's age. And just this month, March, in the *Journal of Clinical Endocrinology and Metabolism*, a wonderful paper was published that provides pediatric age references for serum phosphate, as well as urine calcium/creatinine ratios. So that's pretty much the beginning of our approach.

The next thing is to take a great history. And in a patient who presents with hypocalcemia, the first thing I'll do is look at their neck to see if there is evidence of prior neck or thyroid surgery, since the principal cause of hypoparathyroidism is what I call surgical misadventure. So, either thyroid surgery, cancer surgery of the of the neck, or even parathyroid surgery in the past.

And lastly, in terms of our history, we'll also take a good look at whether there might be other autoimmune or endocrine or other metabolic issues that might constitute a larger syndrome in which hypoparathyroidism is but one component.

Dr. Schweiger:
Sounds great. So, it sounds like there's a few key points when we're evaluating for hypocalcemia. We want to take into account the albumin level and see
that is, and make sure that the value is not affecting the calcium level. And then we want to break the hypocalcemia into two areas, either parathyroid or vitamin D deficiency. And then always making sure to do a good physical exam, especially looking at the thyroid

gland to see if there's been any history of any kind of surgery that could have had effect on the parathyroid hormone.

Dr. Levine:
Exactly. And you know, when we think about the other tests to add, in addition to the 25-Hydroxy vitamin D, we'll also look at a magnesium level, since a low magnesium level or even an elevated magnesium level can cause hypoparathyroidism, or PTH resistance. And that becomes part of the approach as well.

Dr. Schweiger:
That sounds all very helpful. My next question is, you know, are there any other features of ADH1 that can help distinguish it from other causes of hypoparathyroidism?

Dr. Levine:
Well, the biochemical hallmarks of ADH1 are hypocalcemia, which can sometimes be mild, and may even be asymptomatic, and the patient may only be ascertained during routine biochemical screening for some other condition, or even during an annual physical. There's also an elevation in the phosphate level and PTH levels that are low normal, but typically detectable. And that can be confusing, but it's important to remember that a low normal, PTH level in a patient with marked or even moderate hypocalcemia is inappropriate and that should try trigger alarms.

The other thing is the urine calcium level. Urinary calcium reflects not only the filtered load of calcium, so how much calcium gets to the kidney, but also the fractional excretion of calcium. And when serum calcium levels are below 8 mg/dL, there should be very little calcium in the urine. In a patient with ADH1, there can be normal amounts of calcium in the urine, even when the serum calcium levels are less than 8. And this is abnormal, it's unexpected, it's not typical of other forms of hypoparathyroidism. So, this is an important biochemical feature that is unique to ADH1, the fact that you can see an increase in the fractional excretion of calcium in the urine, so that patients who have hypocalcemia will have normal or even elevated urinary calcium levels.

Another feature of ADH1 is type 5 Bartter syndrome. And this occurs in a number of patients who have particular calcium-sensing receptor mutations, and this can be manifest as marked hypomagnesemia and hypokalemia. And there can be many symptoms of hypomagnesemia and hypokalemia that will amplify or magnify the severity of the hypocalcemia.

And then lastly, because there is hypocalcemia and hypomagnesemia, the corrected QT interval, the QTc interval on EKGs is typically prolonged.

I think what's important to appreciate is that ADH1 is the most common form of genetic isolated hypoparathyroidism. So, there is often a family history of either hypocalcemia, hypoparathyroidism, or even renal stones. So, it's important, again, to go back to basics and look at the history carefully.

Dr. Schweiger:
Sounds great. That was a lot of really great information. So, it sounds from that that some of the key points are, you know, taking into account the urine calcium relative to the serum calcium, that even if the urine calcium is falling within the normal range, if it's a patient with hypocalcemia, might be inappropriately normal, and it can still be a mild form of ADH1 and then making sure that we're not missing Bartter syndrome, so also making sure that we're looking at magnesium levels and potassium levels in these patients as well.

Dr. Levine:
Exactly. And you don't even have to get a 24-hour urine collection to look at calcium, although that's the gold standard. Even a random calcium collection, while the patient leaves your office and is on the way to the lab, can be useful looking at either the calcium/creatinine ratio or, what we prefer is the fractional excretion of calcium, and that requires that we know the serum creatinine and serum calcium at the same time that we measure the calcium and creatinine in the urine, and the fractional excretion of calcium will typically be greater than 2% in patients who have ADH1.

Dr. Schweiger:
Wonderful, thank you. Thank you, everyone, for joining us for today's session and wishing everyone a really great day. Thank you.

Announcer:
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