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XLH: An Uncommon But Treatable Disorder

Announcer:
Welcome to CME on ReachMD. This episode is part of our MinuteCME curriculum.

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Dr. Mahan:
My name is John Mahan. I'm a professor of pediatrics at Nationwide Children's Hospital, the Ohio State University College of Medicine. And our topic for today is X-linked hypophosphatemia, an uncommon but treatable disorder. We're going to talk about common symptoms for a uncommon disease, X-linked hypophosphatemia or as I'll refer to it during this presentation XLH. XLH is a X-linked, hereditary progressive and lifelong disorder of renal phosphate wasting. The key element is the renal phosphate wasting, which is present at birth and continues throughout life. It is by far the most common form of heritable hypophosphatemic rickets, and it's been known by patients and healthcare professionals by a number of different terms over the years.

You may have heard terms like X-linked hypophosphatemic rickets, hereditary hypophosphatemic rickets, X-linked rickets, X-linked vitamin D resistant rickets, familial hypophosphatemic rickets. There's a number of terms in the literature. And over the last decade or so, investigators and scholars have really coalesced around this termed X-linked hypophosphatemia because it really describes the major defect, which is the low blood phosphorus levels related to the renal wasting and the fact that it's an X-linked disorder.

And we'll talk about that. The estimated prevalence is about one in 20,000 to one in 25,000 individuals in the United States. And there are thought to be somewhere in the range of 12,000 to 16,000 XLH patients alive today in the United States. There's very little data on variability between populations in other countries or even in parts of the United States. We know the hallmark of X-linked hypophosphatemia is the presence of excess circulating levels in the blood of a important hormone, FGF23.

As we'll talk about this is a phosphaturic hormone. It's devoted to causing renal wasting a phosphorus. And it's really part of our regulatory homeostatic mechanisms to maintain serum calcium and serum phosphorus in the desirable ranges. In this condition, high levels of FGF23 are the problem and are driving the process. We've now come to learn that it's not a defect of FGF23 gene in particular, but a defect of something that regulates FGF23 production, which is called the PHEX gene. PHEX stands for phosphate regulating endopeptidase homolog X-linked.

That's what PHEX stands for. And in the individuals with X-linked hypophosphatemia, there's a loss of function mutation that leads to excess FGF23. So FGF23 is not broken down appropriately. So high circulating levels persist. And the common symptoms and signs of this uncommon disease are really a result of having low phosphorus levels in the blood and all of the downstream effects of that. In children, that involves symptoms like delayed walking and leg pain and clear signs of bone abnormalities such as rickets, which would be evidenced by enlargement of growth plates and metaphases in the knees and wrists in particular, but also disproportionate or impaired growth and craniosynostosis. These symptoms can present as early as the first year of life, and particularly as these kids start to walk is when we notice the rickets changes in the legs, the bowing in particular that occurs as these soft bones, so to speak, are now undergoing stress of walking.

In adults, we've come to appreciate that X-linked hypophosphatemia continues to take its toll. So this is not a condition that gets better over time, but continues to have clinical consequences. And in fact, we've now come to recognize in adults with XLH, many of them are disabled because of their musculoskeletal problems. They continue to have fractures and these things called pseudofractures, which are little hairline fractures through the cortex of the bone, not complete through and through fractures. But these individuals have an increased incidence of osteoarthritis. They can have little osteophytes form at some of their bones surfaces. They can have enthesopathy, which is inflammation and irritation where tendons join bone, and they can develop other significant problems like spinal stenosis, nephrocalcinosis and hearing loss. And then lastly, we see a number of symptoms and signs that really cross between the children and the adults. We see gait abnormalities, bone and joint pain and stiffness, muscle problems in particular, weakness and diminished quality of life in both children and adults with this condition.

And as this condition continues through childhood, these kids do not grow normally on average. So short stature becomes a problem as well as lower limb deformities because of abnormal bone formation, fractures and things like osteomalacia, dental abscesses and caries, which are part of this condition and an increased incidence of chiari malformation and frontal bossing.

So you can see that although these are by themselves signs and symptoms that could be caused by a lot of different conditions, they really characterize a condition that has significant impact on these children and adults in terms of quality of life and particular their musculoskeletal functioning. And as I mentioned, FGF23 is the bad actor. This is a circulating protein, about 250 amino acids with an N-terminal region that contains the active molecule, that's an FGF homology domain. And then a novel C-terminus that has phosphaturic activity that really leads to the phosphate wasting in the kidney.

And it does that by regulating the proximal tubular phosphate resorbers, the sodium phosphate 2A and 2C transporters, and in effect down regulating the expression of these tubular resorbers leading to phosphate loss in the urine. The predominant source of FGF23 in humans is by osteocytes in response to phosphorus levels circulating around and near the osteocytes. But there is also evidence that FGF23 can be secreted from areas of the brain and the thymus. Their crucial role of the excess FGF23 is important to sort of kind of focus on as we understand this disease and the symptoms and signs, but ultimately also the treatment options we have. As I mentioned, the low phosphorus is the key and the elevated FGF23 is the reason for this low phosphorus. As a result of the low phosphorus, what we see is the downregulation of these sodium phosphate tubular resorbers in the proximal tubal leading to renal phosphate wasting.

At the same time, high levels of FGF23 decrease the production of 125 vitamin D in the proximal tubules. That actually down regulates the one hydroxylase enzyme leading to less 125 D, which then causes less GI absorption of phosphorus in the gut. The combination of increased urine losses and decreased GI absorption leads to the abnormal low serum phosphorus and the attendant defective mineralization, delayed ossification, delayed growth and other findings in these individuals.

So, what we've come to appreciate with XLH is really that this is a FGF23 mediated disease. And as we'll talk about, we can understand this condition through that lens and really talk about what are reasonable ways to help these patients have their disease managed and have a better life. So in summary, XLH is a lifelong progressive disorder of phosphate wasting in the kidney driven by elevated levels of FGF23. These individuals with X length hypophosphatemia will have manifestations throughout the life cycle and continue to have a significant burden from this condition. So thank you for attending this session and we appreciate your involvement.

Announcer:
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