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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

XLH: A Case of Bowed Legs - What Else Could It Be?

Announcer:
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Dr. Mahan:
My name is John Mann. I'm a Professor of Pediatrics at Nationwide Children's Hospital, the Ohio State University College of Medicine in Columbus, Ohio. And our case study is one of a case of bowed legs. What else could it be? And don't delay. So this is a young patient of mine who presented at 22 months of age with progressive bowing of his legs. The parents did note some delay in walking compared to what they expected, but the boy had no problems with pain or limitations in his energy level. They did also mention that there was no family history of bowing and he had no other significant medical concerns. As you can see on this x-ray, he has some significant bowing of his femurs as well as his tibias, and some changes at the epiphyses that are consistent with some type of rickets.

So the typical evaluation of a child with evidence of bowing and rickets really involves laboratory studies to look at the calcium phosphorus 1,25 vitamin D PTH axes. And in particular, in this child, his serum phosphorus was low and we had evidence of renal wasting of phosphorus when we did a TmP/GFR, which involves measuring simultaneous serum and urine phosphorus, and serum and urine creatinine. So this child was wasting phosphorus in urine. His 1,25 D level was inappropriately normal. His 25 D level was normal. His alk phos was elevated. His serum calcium was normal, urine calcium normal, and PTH was slightly above the normal range.

In particular in this age group, we worry about nutritional rickets in a child that perhaps is not getting good intake of vitamin D or good intake of calcium, or has problems with absorption of calcium and vitamin D. But as you can see in this chart, we can make a strong case for this kid having something in the X-linked hypophosphatemia pattern because with nutritional rickets, although you would have low phosphorus and low TmP/GFR, you would have low 25 D levels. Again, elevated alk phos, but in particular you would expect to have greatly elevated PTH and potentially even a low serum calcium.

It is important to recognize where the patient's serum phosphorus lies along what's expected in terms of normal for age. So in this kid, for example, we know that this kid's phosphorus level was clearly low, below what it would be expected for a child of two years of age. So a nice way to think about hypophosphatemia when we see this, whether it's in a young child, a child of any age, or even an adult, is to take that low level of serum phosphorus and ask the question, "Is this driven by PTH?" If the PTH is high, then we can focus in on abnormalities and vitamin D metabolism, calcium deficiencies, or primary hyperparathyroidism. If the PTH is normal or low, then we can next focus on whether phosphorus is being lost in the urine and that would be the major driver of the low serum phosphorus.

So for example, if the urine levels of phosphorus are low, we could be talking about insufficient phosphate intake, problems with GI absorption of phosphorus, or enhanced removal of phosphorus from the body, say during a diuresis. In a patient like this where the urine phosphorus levels were high, a serum level of FGF23 can be very valuable. We know that elevated levels of FGF23 are consistent with X-linked hypophosphatemia. So if we see elevated levels of FGF23, then we know we're in this range of X-linked hypophosphatemia or some acquired forms of hypophosphatemic rickets due to high levels of FGF23, like you might see with a tumor.

If, on the other hand, the FGF23 level was normal or low, then you'd be talking about some other rare causes of hypophosphatemia related to increased urine losses. What's important in a patient like this is to make the diagnosis because it really leads to important management considerations. We know that X-linked hypophosphatemia is an abnormality in the PHEX gene. It's inherited in an X-linked dominant manner. We know that these individuals have high levels of FGF23, and nowadays there are gene tests that are relatively easy to obtain that can document the PHEX gene abnormalities to sort of clinch the diagnosis.

We know when a patient is wasting phosphorus to this degree that the blood levels of phosphorus are elevated, and the FGF23 level is elevated, the most likely thing we're going to be dealing with is X-linked hypophosphatemia. We also have come to recognize that 20% to 30% of the cases are not inherited from a parent, but are really spontaneous cases or spontaneous mutations in the PHEX gene. So the absence of a positive family history does not rule out this being a genetic X-linked hypophosphatemia disorder.

It becomes more complex because there now over 700 pathogenic variants the PHEX gene. So it's a really complex gene and many different variations can lead to abnormal PHEX gene activity, which then leads to high circulating levels of FGF23 and the phosphate wasting in the kidney. Why is this important? Because we now have a very effective therapy for XLH. The monoclonal antibody to FGF23, the generic name is Burosumab, effectively decreases the high levels of FGF23 that drives the renal phosphate wasting. And by doing that, really returns the patient to a near normal milieu and allows appropriate mineralization and calcium and phosphorus levels inside muscle and other important cells.

We have every reason to believe that the earlier the intervention, the better the disease control. And I have certainly been lucky enough to have children that presented early in their first two years of life because they had a positive family history. The parents recognized the early signs of this condition, and by treating them early with this effective therapy, have avoided significant bowing. And it is my fondest dream that these kids will never have to develop a personal relationship with an orthopedic surgeon because they're never going to have leg deformities that are going to require orthopedic surgical correction.

We would like to think that this is going to result in better outcomes in the various signs and symptoms that these patients are at risk for in childhood and even into adulthood.And lastly, we now have come to recognize that adults have a significant burden with this disorder of XLH, and therapy like this that returns the serum phosphorus to normal levels appears to be warranted in adults with XLH as well.

So in summary, this condition that this boy had is XLH, which is X-linked hypophosphatemia, which is a hereditary, progressive, lifelong disease.

Again, since 20% to 30% or new mutations, it can be hereditary without a positive family history. And that's where the biochemical studies and the gene tests can be really useful. We know XLH is caused by elevations in FGF23 activity, and the main biochemical findings are the low serum phosphorus, the renal phosphate wasting and the low or inappropriately normal 1,25 vitamin D. And we know even into adulthood, there are problems with bone pain, fractures and pseudo fractures, dental abscesses, osteoarthritis, and muscle pain and weakness. So there is a significant burden even in adults with this condition. So thank you for your attention.

Announcer:
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