

SOME QUESTIONS AND ANSWERS ABOUT XLH

Q. HOW IS XLH RICKETS DIFFERENT FROM OLD-FASHIONED RICKETS?

A: At the turn of the 20th century, many children had rickets because they didn't get enough Vitamin D in their diet or by exposure to enough sunshine. But if you have this so-called Vitamin D-DEFICIENT rickets, as soon as you do get enough Vitamin D back in your diet the bone disease gets better. In XLH, no matter how much Vitamin D is provided in the diet or through the sunshine's effects, the rickets does not get better. This is the reason for one of the early names for XLH: Vitamin D-RESISTANT rickets.



Q. WHAT ARE THE SIGNS AND SYMPTOMS OF XLH?

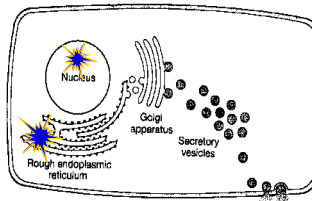
A: The main signs of XLH are low phosphorus in the blood (hypophosphatemia) and bone disease (rickets). Everyone with XLH has hypophosphatemia. Many of those affected with XLH, but not everyone, also have bone disease. On X-rays, this bone disease can easily be identified, but parents may notice early bowing problems when their child begins to walk. Increasingly, dental problems, especially tooth abscesses, are recognised as a common ailment which can occur as a result of XLH. Other possible symptoms are bone pain, as well as muscle pain and weakness.



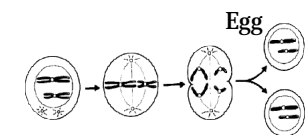
Q. SO WHAT IS CAUSING THE SYMPTOMS OF XLH?

A: XLH is a genetic (inherited) metabolic bone disease where the mechanisms that control the body's ability to make and maintain bones (and teeth) are not working correctly. One of the things needed for good bone metabolism is the mineral phosphorus. The key feature of XLH -- low phosphorus or hypophosphatemia -- is the result of a mutation (change) in one of the genes on the X chromosome. When this gene, the PHEX gene, has the XLH mutation, bone cells are unable to produce an enzyme which is a crucial cog in the biochemical machinery that maintains the blood's proper level of phosphorus. This system is still not fully understood.

Protein Production in the Bone Cell

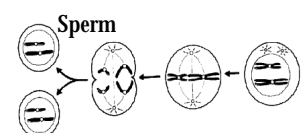


But when this biochemical process is unable to work properly, the kidneys will leak phosphorus into the urine instead of keeping it in the body. This is the problem that causes the hypophosphatemia seen in XLH. The other aspect of XLH is bone disease or rickets. Not everyone with XLH has rickets and those who do may have symptoms ranging from mild to severe. Since everyone with XLH has hypophosphatemia, other factors besides the low phosphorus must be contributing to the varying rickets symptoms. These other factors and the wide variability in severity of bone disease are not yet fully understood and are still being studied by researchers.



Q. HOW DOES THE DISEASE GET PASSED ON TO CHILDREN?

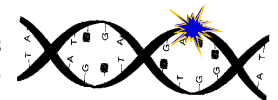
A: Each of us has a pair of sex chromosomes, of which at least one is the X chromosome; girls have two X's, while boys have one X and one Y. Each child gets one of its mother's X chromosomes. Girls get their father's X while boys get their father's Y. Since the XLH



gene is on the X chromosome, if a father has XLH his one X chromosome has the XLH mutation. Each of his children gets either his X or his Y. Children who get his X will have inherited his XLH gene and will have the disease. It's like tossing a coin; 2 choices, X or Y, XLH or not XLH. The odds are 50-50 for each child. It just so happens that those who get their father's X chromosome will also be girls. Thus all of his daughters will have XLH, but none of his sons. If a mother has XLH, one of her X chromosomes has the XLH gene and the other probably doesn't. Each of her children gets exactly one of her X's, so some get the XLH-free one and some get the one with XLH. Again, it's like tossing a coin: 2 choices, X with XLH or X without XLH. The odds are still 50-50 for each child. The only difference is that a mother can pass the XLH gene to either sons or daughters. Another genetic bone disease, called Autosomal Dominant Hypophosphatemic Rickets, has characteristics similar to XLH but the mutation is not on the X (or Y) chromosomes. As with XLH, each child would have a 50-50 chance of inheriting this mutated gene from either parent, but since the mutation is not on the sex chromosomes, either boys or girls could get the gene from their mother or their father. Professional genetics counselling is always advisable in any case.

Q. CAN SOMEONE HAVE XLH WHEN IT HAS NEVER OCCURRED IN THE FAMILY BEFORE?

A: First, you may think it has never occurred before when it actually was there. Remember that not everyone with XLH gets bone disease. In general, women as a group seem to have milder rickets symptoms or no rickets at all even when they have the low phosphorus of XLH. Just looking for bone disease is not enough. Other tests, including a blood test to check for the low phosphorus level, would have to be done to really be sure earlier generations did not have XLH. Secondly, it is possible for XLH to have truly never occurred before it affects a new person. The change to the X chromosome that causes XLH can suddenly occur when an egg or sperm cell is formed, even though the mutation wasn't there in the parents' X chromosomes. Mutations have to begin somewhere, and this is how it can happen. Once it appears, it may then be passed on to later generations. Thirdly, although unlikely, there is an extremely rare benign bone tumour which causes rickets symptoms, and if there is no family history of low phosphorus and rickets, your doctor will want to rule out the possibility of such a tumour.



Q. IS XLH CURABLE?

A: No. The mechanisms of this disease are not yet fully understood, and thus there is not yet a curative treatment. But the gene that carries the XLH mutation has only recently been identified and research continues. There are important advances in research happening right now, and the XLH Network is actively informed by some of the world's leading researchers. One day, we hope that greater understanding will lead to a cure.



Q. IS XLH TREATABLE?

A: There are treatments that can help in many, but not all, cases. Current medical therapy typically consists of daily doses of a special type of Vitamin D and an oral phosphate (phosphorus) preparation. Currently these are the medications that can provide phosphorus for the best possible bone development in XLH, though often it is not feasible to achieve normal blood phosphorus levels. For young children with XLH this is sometimes enough to keep any rickets symptoms from developing, or from being too bad, or even to straighten still-growing legs that had already become bent. Some newer medications, still in the research stage, also seem promising for some cases. However, even with the best medication and monitoring, sometimes more severe rickets will still develop. Then, orthopedic surgery may be recommended to straighten the bowed or knock-kneed legs. Because of the variability of symptoms, each case is unique and must be treated individually. In general however, the earlier a diagnosis can be confirmed and therapy started, the better the results may be. Since some side effects of the medication can be serious, continual monitoring is very important. In this respect also each case is unique and must be followed individually. Because of any treatment's possible long-term effects there is some question about how long medical therapy should continue, and whether adults with XLH should start or continue using these medications. But as long as careful monitoring is maintained, adult treatment can be advisable to help relieve symptoms.

