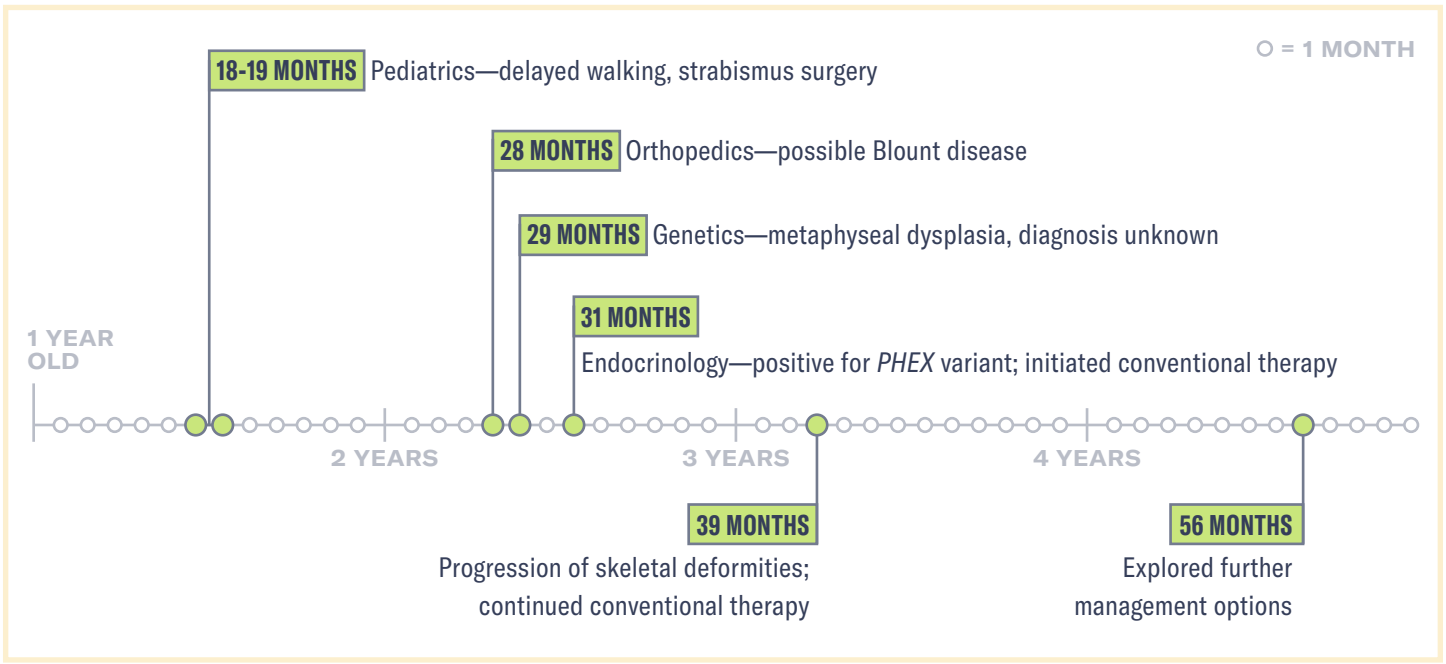
4-year-old female with spontaneous XLH*



Case summary

Findings/outcomes

- The patient was seen by multiple specialists and after referral to an endocrinologist, a conclusive diagnosis was not reached over a period of 13 months; the patient's case was subsequently followed by a nephrologist
- **Disease symptoms of patient continued to progress** despite therapy with oral calcitriol and potassium phosphate

Although X-linked hypophosphatemia (XLH) is primarily an inherited disease, 20% to 30% of cases arise spontaneously.[1,2]

*The information for this case study was provided courtesy of Dr. Anthony Portale, Director of the Pediatric Dialysis Program, UCSF Benioff Children's Hospital, San Francisco. This case study represents a real patient and is intended to be illustrative, not a recommendation for treatment or management. This case study does not claim to represent typical results.

Medical history

18-19 months: Pediatric evaluation

- 18-month-old female presented with leg bowing, wide-based gait, delayed walking, and poor growth; fear of climbing stairs
- X-rays: indicative of metaphyseal dysplasia
- Other clinical findings: strabismus, suspected to contribute to walking delay; underwent strabismus surgery

28 months: Orthopedic evaluation

- Physical exam: short stature, height less than 5th percentile since age 15 months (see Growth chart below); worsened bowing and waddling gait
- X-rays: significant bilateral genu varum with mild beaking and sloping of the proximal tibial metaphysis; metaphyseal-diaphyseal angles of bilateral proximal tibiae measured 16 degrees; bilateral irregularity of the distal femoral metaphysis also noted; femoral heads were normally located
- Differential diagnosis: possible Blount disease, metaphyseal dysplasia, or physiologic genu varum

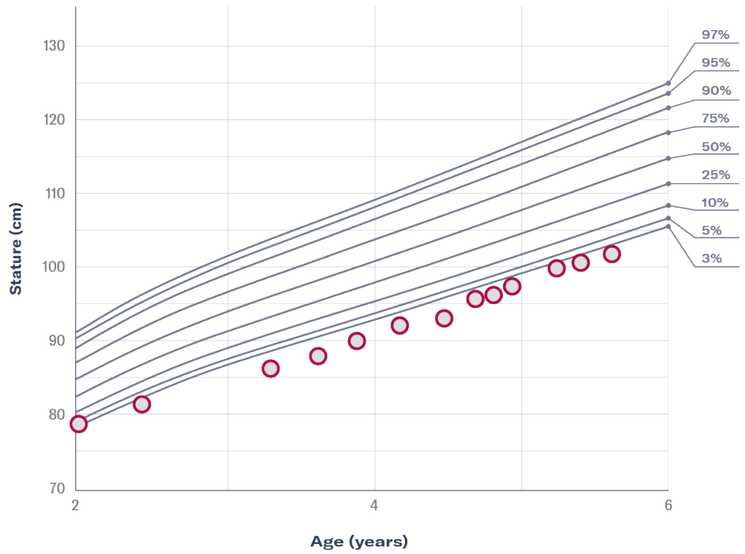
29 months: Genetics evaluation

- No family history of bone disease
- Suspected diagnosis: metaphyseal dysplasia
- Underwent genetic testing for Schmid metaphyseal chondrodysplasia and Shwachman-Diamond syndrome; results were negative for pathologic variants
- Diagnosis: unknown, referred to skeletal dysplasia clinic

31 months: Endocrinology evaluation

- Physical exam: bilateral genu varum
- X-rays: bilateral mild coxa vara, tibial varus (left greater than right) with metaphyseal irregularity and fraying of the distal femur, tibia, and ulna; metaphyseal widening at wrists
- See Laboratory test results on back
- Other findings: 2nd percentile for weight; 1st percentile for height (see Growth chart below)

Growth chart: Stature for age percentiles, girls aged 2-6 years[3†]



History of growth progression:

- Patient had short stature
- At 31 months, the patient was in the 1st percentile for height

†The reference percentiles on the graph are combined from the 2 clinical growth charts for girls 2-20 years of age provided by the Centers for Disease Control and Prevention.

Diagnosis and initial treatment

31 months

- Hypophosphatemic rickets; positive for *PHEX* mutation; negative in parents—spontaneous XLH
- Treatment: oral calcitriol and potassium phosphate

For patients with XLH, the diagnosis process can be long and laborious, and proper specialist referral can be key to early disease management.

Disease progression

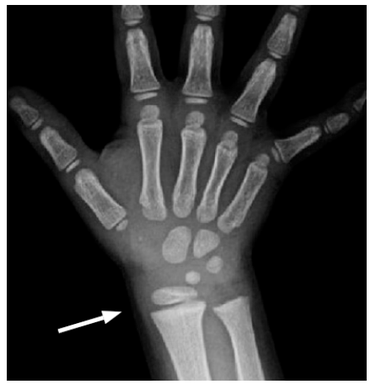
39 months: Nephrology follow-up evaluation

- Patient continued to take oral calcitriol and potassium phosphate
- Physical exam: wide-based gait; mild genu varum; intercondylar distance 1.0 cm; bilateral mild tibial bowing
- X-rays: mild metaphyseal fraying at distal radius and ulna; metaphyseal widening and fraying at distal femur and proximal tibia (see X-rays 1-3)

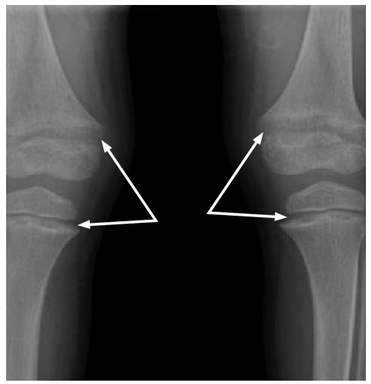
54 months

- Further management options explored due to continued disease progression
- See Laboratory test results on back

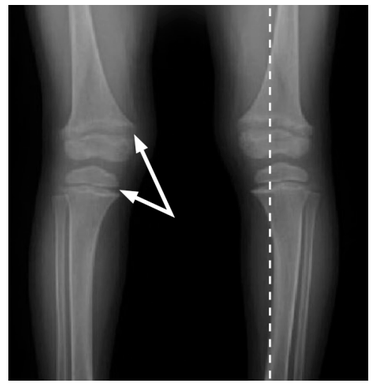
X-ray 1: Right wrist



X-ray 2: Knees



X-ray 3: Legs



54 months: mild metaphyseal fraying at the bilateral distal radius and ulna, and to a lesser extent of the bilateral distal femoral metaphyses.

XLH LINK

Laboratory test results

This patient's disease symptoms continued to progress despite therapy with oral calcitriol and potassium phosphate.

Test (reference range‡ unit)	**31 months** (results)	**54 months** (results)
Serum phosphorus (4.3-6.8 mg/dL)	**2.9**	**2.5**
TmP/GFR (4.0-5.2 mg/dL)	**2.4**	n/a
25(OH)D (≥20 ng/mL)	41	31
ALP (<156-369 U/L)	**461**	**404**
Serum calcium (9.2-10.5 mg/dL)	9.4	9.9
PTH (<10-65 pg/mL)	57	31

‡Indicates normal range, age and sex matched. Note that normal range values may vary depending on reference dataset. The ranges in this table were provided by the treating physician. Colored values are outside of the normal range provided by the physician and can raise suspicion of XLH.

25(OH)D=25-hydroxyvitamin D; ALP=alkaline phosphatase; PTH=parathyroid hormone; TmP/GFR=ratio of tubular maximum reabsorption of phosphate to glomerular filtration rate.

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1. Dahir K, Roberts MS, Krolczyk S, Simmons JH. X-linked hypophosphatemia: a new era in management. *J Endocr Soc.* 2020;4(12):bvaa151. doi:10.1210/jendso/bvaa15 **2.** Gaucher C, Walrant-Debray O, Nguyen TM, Esterle L, Garabédian M, Jehan F. *PHEX* analysis in 118 pedigrees reveals new genetic clues in hypophosphatemic rickets. *Hum Genet.* 2009;125(4):401-411. doi:10.1007/s00439-009-0631-z **3.** Centers for Disease Control and Prevention. Clinical growth charts. 2 to 20 years: girls. Published May 30, 2000. Accessed May 21, 2019. https://www.cdc.gov/growthcharts/data/set2clinical/cj41c072.pdf

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