X-linked hypophosphatemia

X-linked hypophosphatemia (XLH) is an inherited disorder characterized by low levels of phosphate in the blood. Phosphate levels are low because phosphate is abnormally processed in the kidneys, which causes a loss of phosphate in the urine (phosphate wasting) and leads to soft, weak bones (rickets)

XLH patients may also be affected by premature, complete, or partial ossification of sutures between cranial bone, which could eventually result in cranial dysmorphia, decreased intracranial volume, and secondary abnormally high intracranial pressure with a cerebral compression. Our goal is to address the criteria and the management of the skeletal complications associated with XLH, mainly orthopedic and neurosurgical care, and reflect on decision-making and follow-up complexities. [1)].

Craniosynostosis is an underdiagnosed complication of hypophosphatemic rickets. Many patients with normal head size and growth may go undiagnosed, thus it is important to consider this association for early diagnosis and possible surgical treatment. A multidisciplinary approach is necessary for a correct long-term follow-up. [2)].

A 7 year-old twin girl with hypophosphataemic rickets was evaluated for a recent onset of mild strabismus.She was a homozygous twin sister with hypophosphataemic rickets diagnosed at the age of 2 years, with a mutation in intron 21 of the PHEX gene, which was also present in her sister.The girls' clinical histories were remarkable for an important lower limb varus that progressively improved after starting phosphate supplementation with a galenical solution (Joulies solution 1 mmol phosphate/ml) and vitamin D 1,25 OH.During the examinations, both girls were in good general condition. Physical examinations were unremarkable, except for tibial varus, bilateral fifth finger clinodactyly and bilateral syndactyly of the third and fourth foot fingers. No major head shape abnormalities were noticeable except for a high forehead.One patient presented with a slight strabismus, normal isochoric isocyclic and reactive pupils, no signs of cranial nerve deficit, and no alterations in the rest of the neurological examination. An ophthalmological evaluation showed bilateral papilloedema. A cerebral MRI scan was then performed, suspecting elevated intracranial pressure (figure 1). The same examination was performed on the asymptomatic sister which also demonstrated papilloedema with similar findings on cranial MRI too.
edpract;107/2/124/BLKF1F1BLK_F1Figure 1Sagittal MR T1-weighted imaging shows a 12 mm cerebellar tonsillar herniation (shown by the white arrow) and bulb-medullary junction herniation. The apex of the epistropheus tooth almost reaches the occipital clivus (shown by the white line) and imprints the bulb. QUESTIONS: Which is the most likely diagnosis?CraniosynostosisPseudotumor cerebriDrusenArnold-Chiari malformationHow should these patients be managed?Acetazolamide treatmentThird to fourth ventricle cystostomyWait and see with periodical visual evoked potential follow-upNeurosurgeryHow should patients with X linked hypophosphataemic rickets (XLH rickets) be managed for the risk of craniosynostosis?Monitor cephalic anthropometric measuresPerform a MRI scan if clinical signs of craiosynostosis or intracranial hypertension are presentPerform a skull X-ray every 2 yearsPerform an MRI scan every 2 years [3)].

Careful monitoring of head shape and growth is therefore critical for early detection of

craniosynostosis in XLH. [4)]

Rothenbuhler et al. found that 59% of XLHR children had a complete or partial fusion of the sagittal suture and 25% of XLHR children showed protrusion of the cerebellar tonsils. A history of dental abscesses was associated with craniosynostosis, and craniosynostosis was associated with abnormal descent of cerebellar tonsils. Only 2 patients showed neurologic symptoms. Four of 44 patients (9%) required neurosurgery. This study highlights that sagittal suture fusion and Chiari type I malformation are frequent complications of XLHR. The incidence of sagittal synostosis in XLHR is actually extremely high and was probably underestimated so far. Chiari type I malformation is also frequent. Because diagnosis of craniovertebral anomalies can be underestimated on a purely clinical basis, radiological studies should be considered in XLHR children if a proper diagnosis is warranted. [5)].

X-linked hypophosphatemia (XLH) is the most common inherited form of renal phosphate wasting and inherited rickets. Patients have hyperplasia of fibrochondrocytes in tendons and ligaments, causing the structures to thicken and calcify. Thickening of the lamina, hypertrophy of facet joints, and calcification of spinal ligaments are sequelae of this condition and can result in central or foraminal stenosis that compresses nerve roots or the spinal cord [6)].

14: Ellis MB, Gridley D, Lal S, Nair GR, Feiz-Erfan I. Phosphaturic mesenchymal tumor of the brain without tumor-induced osteomalacia in an 8-year-old girl: case report. J Neurosurg Pediatr. 2016 May;17(5):573-7. doi: 10.3171/2015.9.PEDS14617. Epub 2016 Jan 1. PMID: 26722864.

15: Jaszczuk P, Rogers GF, Guzman R, Proctor MR. X-linked hypophosphatemic rickets and sagittal craniosynostosis: three patients requiring operative cranial expansion: case series and literature review. Childs Nerv Syst. 2016 May;32(5):887-91. doi: 10.1007/s00381-015-2934-9. Epub 2015 Oct 28. PMID: 26510652.

16: Freudlsperger C, Hoffmann J, Castrillon-Oberndorfer G, Engel M. Bilateral coronal and sagittal synostosis in X-linked hypophosphatemic rickets: a case report. J Craniomaxillofac Surg. 2013 Dec;41(8):842-4. doi: 10.1016/j.jcms.2013.01.039. Epub 2013 Mar 7. PMID: 23466123.

17: Pirola E, Vergani F, Casiraghi P, Leone EB, Guerra P, Sganzerla EP. Oncogenic osteomalacia caused by a phosphaturic mesenchymal tumor of the thoracic spine. J Neurosurg Spine. 2009 Apr;10(4):329-33. doi: 10.3171/2009.1.SPINE08351. PMID: 19441990.

18: Murthy AS. X-linked hypophosphatemic rickets and craniosynostosis. J Craniofac Surg. 2009 Mar;20(2):439-42. doi: 10.1097/SCS.0b013e31819b9868. PMID: 19242361.

19: Yoshioka K, Nagata R, Ueda M, Yamaguchi T, Konishi Y, Hosoi M, Inoue T, Yamanaka K, Iwai Y, Sato T. Phosphaturic mesenchymal tumor with symptoms related to osteomalacia that appeared one year after tumorectomy. Intern Med. 2006;45(20):1157-60. doi: 10.2169/internalmedicine.45.1797. Epub 2006 Nov 15. PMID: 17106161.

20: Soehle M, Casey AT. Cervical spinal cord compression attributable to a calcified intervertebral disc in a patient with X-linked hypophosphatemic rickets: case report and review of the literature. Neurosurgery. 2002 Jul;51(1):239-42; discussion 242-3. doi: 10.1097/00006123-200207000-00038. PMID: 12182425.

21: Zoidis E, Gosteli-Peter M, Ghirlanda-Keller C, Meinel L, Zapf J, Schmid C. IGF-I and GH stimulate Phex mRNA expression in lungs and bones and 1,25-dihydroxyvitamin D(3) production in hypophysectomized rats. Eur J Endocrinol. 2002 Jan;146(1):97-105. doi: 10.1530/eje.0.1460097. PMID: 11751074.

22: Yoshida T, Yoshida N, Monkawa T, Hayashi M, Saruta T. Dietary phosphorus deprivation induces 25-hydroxyvitamin D(3) 1alpha-hydroxylase gene expression. Endocrinology. 2001 May;142(5):1720-6. doi: 10.1210/endo.142.5.8119. PMID: 11316734.

23: Velan GJ, Currier BL, Clarke BL, Yaszemski MJ. Ossification of the posterior longitudinal ligament in vitamin D-resistant rickets: case report and review of the literature. Spine (Phila Pa 1976). 2001 Mar 1;26(5):590-3. doi: 10.1097/00007632-200103010-00029. PMID: 11242392.

24: Zoidis E, Zapf J, Schmid C. Phex cDNA cloning from rat bone and studies on phex mRNA expression: tissue-specificity, age-dependency, and regulation by insulin-like growth factor (IGF) I in vivo. Mol Cell Endocrinol. 2000 Oct 25;168(1-2):41-51. doi: 10.1016/s0303-7207(00)00310-5. PMID: 11064151.

25: Kuether TA, Piatt JH. Chiari malformation associated with vitamin D-resistant rickets: case report. Neurosurgery. 1998 May;42(5):1168-71. doi: 10.1097/00006123-199805000-00134. PMID: 9588565.

26: Roy S, Martel J, Tenenhouse HS. Growth hormone normalizes renal 1,25-dihydroxyvitamin D3-24-hydroxylase gene expression but not Na+-phosphate cotransporter (Npt2) mRNA in phosphate-deprived Hyp mice. J Bone Miner Res. 1997 Oct;12(10):1672-80. doi: 10.1359/jbmr.1997.12.10.1672. PMID: 9333128.

27: Vera CL, Cure JK, Naso WB, Gelven PL, Worsham F, Roof BF, Resnick D, Salinas CF, Gross JA, Pacult A. Paraplegia due to ossification of ligamenta flava in X-linked hypophosphatemia. A case report. Spine (Phila Pa 1976). 1997 Mar 15;22(6):710-5. doi: 10.1097/00007632-199703150-00027. PMID: 9089946.

28: Dunlop DJ, Stirling AJ. Thoracic spinal cord compression caused by hypophosphataemic rickets: a case report and review of the world literature. Eur Spine J. 1996;5(4):272-4. doi: 10.1007/BF00301332. PMID: 8886741.

29: Ballantyne ES, Findlay GF. Thoracic spinal stenosis in two brothers due to vitamin D-resistant rickets. Eur Spine J. 1996;5(2):125-7. doi: 10.1007/BF00298392. PMID: 8724193.

30: Yamamoto Y, Onofrio BM. Spinal canal stenosis with hypophosphatemic vitamin D-resistant rickets: case report. Neurosurgery. 1994 Sep;35(3):512-4; discussion 514-5. doi: 10.1227/00006123-199409000-00022. PMID: 7800144.

31: Bussière JL, Ristori JM, Miravet L, Piat C, Soubrier M, Bardin T. Rachitisme vitamino-résistant hypophosphatémique et compression médullaire. A propos de deux cas [Vitamin-resistant hypophosphatemic rickets and spinal cord compression. Apropos of 2 cases]. Rev Rhum Ed Fr. 1993 Jan;60(1):64-8. French. PMID: 8242029.

1)
Rocco FD, Rothenbuhler A, Adamsbaum C, Bacchetta J, Pejin Z, Finidori G, Pannier S, Linglart A, Wicart P. Orthopedic and neurosurgical care of X-linked hypophosphatemia. Arch Pediatr. 2021 Oct;28(7):599-605. doi: 10.1016/j.arcped.2021.09.003. Epub 2021 Oct 6. PMID: 34625380.

2)
Arenas MA, Jaimovich S, Perez Garrido N, Del Pino M, Viterbo G, Marino R, Fano V. Hereditary

hypophosphatemic rickets and craniosynostosis. J Pediatr Endocrinol Metab. 2021 Jun 21;34(9):1105-1113. doi: 10.1515/jpem-2021-0042. PMID: 34147045.

3) Migliarino V, Magnolato A, Barbi E. Twin girls with hypophosphataemic rickets and papilloedema. Arch Dis Child Educ Pract Ed. 2022 Apr;107(2):124-126. doi: 10.1136/archdischild-2020-319615. Epub 2020 Oct 30. PMID: 33127660.

4) Lee KS, Lee BL. The first Korean case report with scaphocephaly as the initial sign of X-linked hypophosphatemic rickets. Childs Nerv Syst. 2019 Jun;35(6):1045-1049. doi: 10.1007/s00381-018-04042-7. Epub 2019 Jan 6. PMID: 30613854.

5) Rothenbuhler A, Fadel N, Debza Y, Bacchetta J, Diallo MT, Adamsbaum C, Linglart A, Di Rocco F. High Incidence of Cranial Synostosis and Chiari I Malformation in Children With X-Linked Hypophosphatemic Rickets (XLHR). J Bone Miner Res. 2019 Mar;34(3):490-496. doi: 10.1002/jbmr.3614. Epub 2018 Nov 20. PMID: 30352126; PMCID: PMC7816089.

6) Riccio AR, Entezami P, Giuffrida A, Dowling J, Forrest G, German JW. Minimally Invasive Surgical Management of Thoracic Ossification of the Ligamentum Flavum Associated with X-linked Hypophosphatemia. World Neurosurg. 2016 Oct;94:580.e5-580.e10. doi: 10.1016/j.wneu.2016.07.076. Epub 2016 Jul 30. PMID: 27481600.