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CASE REPORT

The first Korean case report with scaphocephaly as the initial sign of X-linked hypophosphatemic rickets

Keun Soo Lee[1] · Bo Lyun Lee[2]

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Abstract

Introduction X-linked hypophosphatemic rickets (XLH) can occasionally cause premature fusion of cranial sutures through an increased level of fibroblast growth factor 23 (FGF-23), which leads to the dysregulation of phosphate and vitamin D metabolism. Secondary craniosynostosis has long been considered to present late after XLH has already been diagnosed either clinically or genetically.

Case presentation We present observations of a male infant showing sagittal synostosis as the first sign of XLH. Our patient did not show any other skeletal deformities except macrocephaly with a long head shape. There is a family history of genetically unconfirmed hypophosphatemic rickets in his mother. Direct sequencing by genomic polymerase chain reaction revealed that the patient has a large deletion comprising exons 1–3 of the phosphate regulating endopeptidase homolog X-linked (*PHEX*) gene.

Conclusion Our observations suggest that craniosynostosis secondary to rickets can develop in early infancy. Careful monitoring of head shape and growth is therefore critical for early detection of craniosynostosis in XLH.

Keywords Craniosynostosis · X-linked hypophosphatemic rickets · *PHEX*

Introduction

X-linked hypophosphatemic rickets (XLH) is a rare disease that is caused by loss-of-function mutations in the phosphate-regulating endopeptidase homolog X-linked (*PHEX*) gene, resulting in renal phosphate loss and bone hypomineralization [1]. Typical clinical features of this disease include leg bowing, short stature, and bone pain [1, 2]. Clinical diagnosis of XLH is typically possible in children around 2 years of age, after noticing short stature and bowed legs, observed once the child is walking [1]. Craniosynostosis has also been reported as a late-presenting sign of rickets usually not seen in infancy [3]. Early progression of closing cranial sutures has been rarely reported in XLH [4]. Here, we report the first case of an infant with sagittal synostosis as an initial indicator of XLH associated with a large deletion in the *PHEX* gene.

✉ Bo Lyun Lee
bototii@paik.ac.kr

[1] Department of Neurosurgery, Busan Paik Hospital, Inje University College of Medicine, Busan, South Korea

[2] Division of Pediatric Neurology, Department of Pediatrics, Busan Paik Hospital, Inje University College of Medicine, Bokji-ro 75, Busanjin-gu, Busan 47392, South Korea

Case description

An 11-month-old boy was referred to our clinic for an abnormal long head shape. Clinical examination revealed scaphocephaly (cephalic index 0.67), a large head circumference (50.8 cm, > 99th percentile) (Fig. 1). He was diagnosed with sagittal synostosis (Fig. 2). The patient was born without perinatal problems after 38 weeks of gestation. At birth, he had a mildly elongated head shape but a normal head circumference (36 cm, 75–90th percentile). He had a family history of hypophosphatemic rickets in his mother, who had been treated with oral phosphate and calcitriol and corrective surgery on her bowed leg. Other than his mother, he had no family history of rickets. His mother's head shape was normal. No *PHEX* mutations were identified by direct sequencing of polymerase chain reaction (PCR) using the mother's genomic DNA prior to her pregnancy. She was diagnosed with sporadic hypophosphatemic rickets without genetic confirmation. However, in our patient, PCR products corresponding to exons 1–3 of *PHEX* were not detected (Fig. 3), suggesting that these exons are deleted. These results demonstrate that our patient is hemizygous while his mother may be heterozygous for the deletion of *PHEX*.

At diagnosis of his craniosynostosis, the patient showed normal stature and development without leg

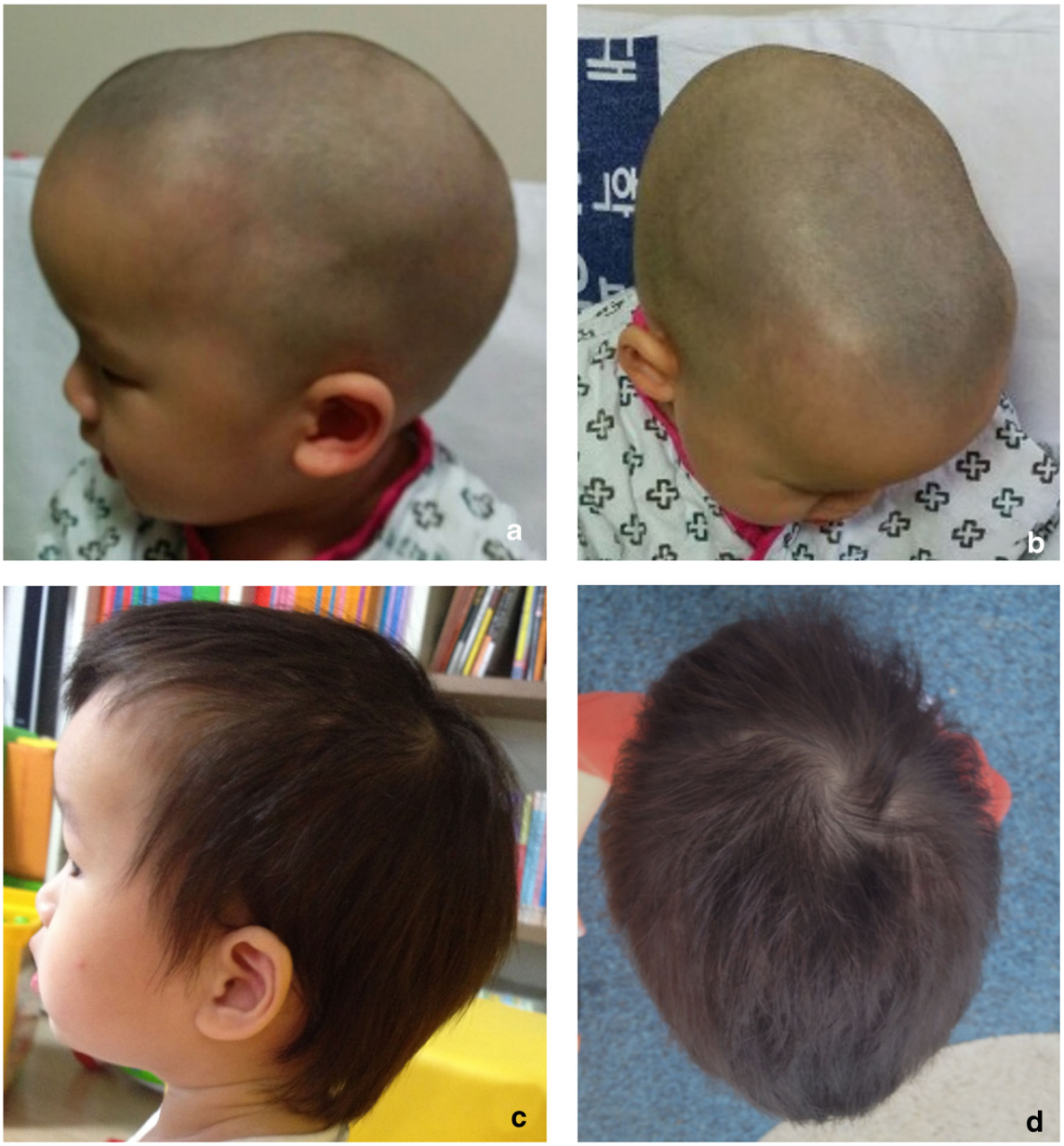

Fig. 1 **a**, **b** Preoperative photograph at age 12 months showing typical scaphocephaly. **c**, **d** Photograph after cranial vault remodeling surgery, revealing improved head shape at age 18 months

deformities. Laboratory results showed a normal serum calcium level of 10.0 mg/dL (normal range, 8.8–10.8) and a mildly decreased phosphorus level of 3.0 mg/dL (normal range, 3.8–6.5). The tubular reabsorption rate of phosphate was decreased by 64% (normal range, 85–100). The plain films of the patient's leg revealed mild metaphyseal fraying without bowing.

Since his diagnosis with XLH, the patient has been treated with alfacalcidol and oral phosphate. He underwent cranial vault remodeling surgery at 12 months of age. He had a post-operative cephalic index of 0.74 and his cranial shape was improved (Fig. 1). His development remains normal with stable head growth at age of 4.5 years (Fig. 4).

Discussion

We described an infant case with early presentation of craniosynostosis in XLH. In our patient, the initial sign of rickets was scaphocephaly with no other bone deformities. Congenital craniosynostosis is usually diagnosed in infancy due to early progression of head dysmorphology, while hypophosphatemic rickets shows a significant delay in presentation of synostosis, which is usually observed between 2 and 4 years of age [3, 5–7]. Only rarely the diagnosis of premature fusion of cranial sutures precedes that of XLH rickets [4], and no case has yet been reported in Korea. Our patient also presented macrocephaly owing to compensatory growth

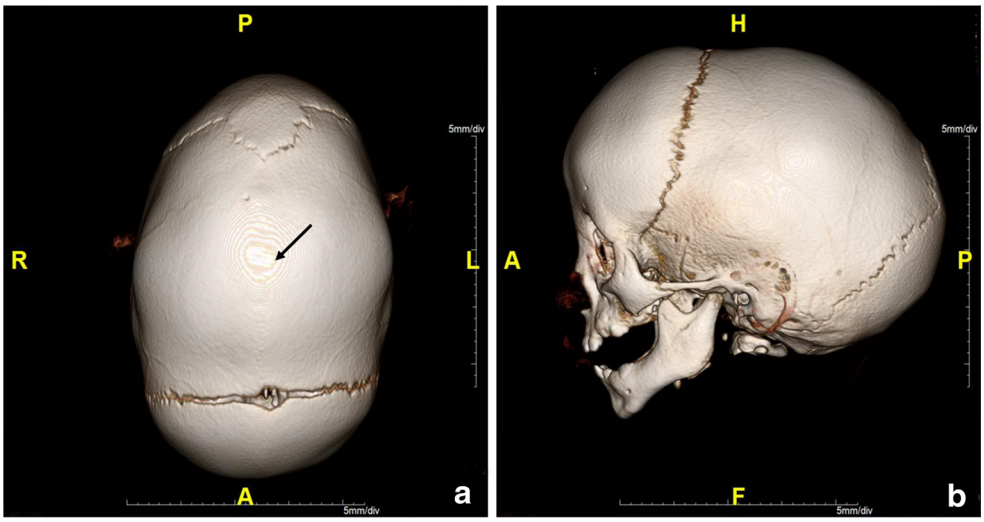

Fig. 2 Identification of sagittal synostosis on a three-dimensional computerized tomography scan reconstruction at age 11 months. Imaging shows a fused sagittal suture (**a**, arrow) and scaphocephaly and posterior reduction in skull height (**b**)

occurring anteroposteriorly in response to the diminished posterior skull height in sagittal synostosis [8]. His macrocephaly has been gradually resolving after skull remodeling operation.

The exact incidence of craniosynostosis in XLH is not yet known. Willis et al. [9] reviewed the reported data on pediatric cases of XLH, and craniosynostosis was documented in 12.1% (19/157) of patients. Currarino [6] demonstrated a 46.4% radiographic incidence of craniosynostosis and Rothenbuhler et al. [10] found that 59% of XLH children had sagittal synostosis in hypophosphatemic rickets. Sagittal synostosis was reported as the most common type and was seen exclusively in boys [7, 9]. Our patient was also male, and his mother did not show the head dysmorphology. The gender discrepancy of craniosynostosis may be related to the severe phenotype in males with X-linked dominant disease [7, 9]. However, it has not been validated thus far that males are usually more severely affected with XLH [11].

Fig. 3 Analysis of the *PHEX* gene by genomic PCR, showing deletion of exons 1–3 when compared with control exons (C-1, C-2, C-3)

The exact pathomechanism of the premature fusion of cranial sutures in XLH is not well understood. According to animal studies, *PHEX* dysfunction leads to an excess of circulating fibroblast growth factor (FGF) 23, which in turn results in cross-binding with FGF receptors 2 and 3 expressed in osteoblasts of the skull, leading to craniosynostosis [12, 13]. Activating mutations of these FGF receptors have been well documented in syndromic craniosynostosis [14]. Considering this mechanism, early treatment with anti-FGF23 antibody, which was approved as a promising drug, would be anticipated to prevent craniosynostosis as well as leg deformities [15].

In this case, a large deletion comprising exons 1–3 of *PHEX* was detected. This has been previously reported as a causative mutation of XLH [2]. However, craniosynostosis has not been reported in patients with this same deletion. This indicates that the type of *PHEX* mutation may have limited predictive value for the XLH phenotype [2, 11, 16, 17]. This suggests that environmental and other genetic factors may affect the phenotypes of patients with XLH [2, 11].

Most children with XLH are asymptomatic in infancy because progressive leg deformities and decreased linear growth tend to be noticed after the child is weight-bearing. Furthermore, craniosynostosis has been considered as a late presentation that should be monitored after a diagnosis of rickets. However, our case showed that craniosynostosis can be the first sign of XLH before other skeletal deformities become apparent. Therefore, we suggest that infants with craniosynostosis should be screened for hypophosphatemic rickets. It is possible that some craniosynostosis in XLH remained undetected, especially considering the relatively high incidence. We also recommend that head shape and growth should be monitored from early infancy in all patients with XLH or a family history of rickets.

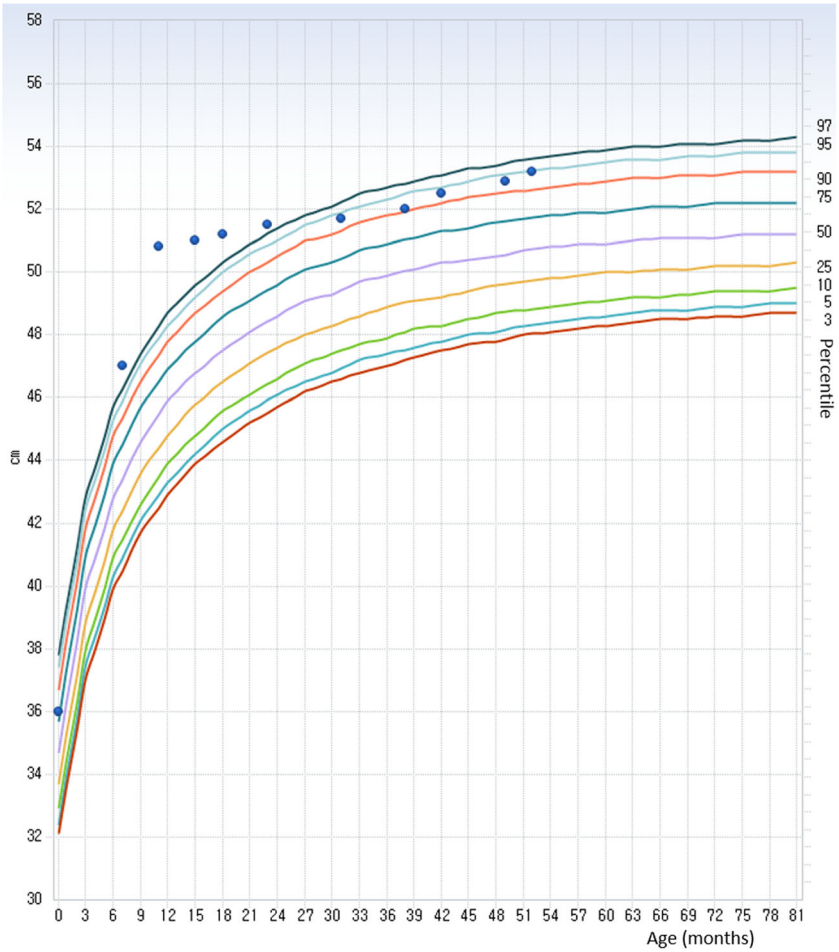

Fig. 4 Nomogram for fronto-occipital circumference of our patient reveals macrocephaly (head circumference *z* score + 3.6 SD) at 11 months of age when he was diagnosed with sagittal synostosis. After cranial vault remodeling surgery, his large head circumference has been gradually resolving as overall skull height has increased. His head circumference is 52.7 cm, between the 90th and 95th percentiles (*z* score was + 1.38 SD) at age of 4.5 years

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Compliance with ethical standards

Conflict of interest The authors declare no potential conflicts of interest with respect to the research, authorship, or publication of this article.

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References

1. Capelli S, Donghi V, Maruca K, Vezzoli G, Corbetta S, Brandi ML, Mora S, Weber G (2015) Clinical and molecular heterogeneity in a large series of patients with hypophosphatemic rickets. Bone 79: 143–149. https://doi.org/10.1016/j.bone.2015.05.040
2. Holm IA, Nelson AE, Robinson BG, Mason RS, Marsh DJ, Cowell CT, Carpenter TO (2001) Mutational analysis and genotype-phenotype correlation of the PHEX gene in X-linked hypophosphatemic rickets. J Clin Endocrinol Metab 86(8):3889–3899. https://doi.org/10.1210/jcem.86.8.7761
3. Murthy AS (2009) X-linked hypophosphatemic rickets and craniosynostosis. J Craniofac Surg 20(2):439–442. https://doi.org/10.1097/SCS.0b013e31819b9868
4. Vakharia JD, Matlock K, Taylor HO, Backeljauw PF, Topor LS (2018) Craniosynostosis as the presenting feature of X-linked rickets. Pediatrics 141(Suppl 5):S515–S519. https://doi.org/10.1542/peds.2017-2522
5. Seruya M, Oh AK, Boyajian MJ, Myseros JS, Yaun AL, Keating RF, Rogers GF (2013) Age at initial consultation for craniosynostosis: comparison across different patient characteristics. J Craniofac Surg 24(1):96–98. https://doi.org/10.1097/SCS.0b013e318270fb83
6. Currarino G (2007) Sagittal synostosis in X-linked hypophosphatemic rickets and related diseases. Pediatr Radiol 37(8):805–812. https://doi.org/10.1007/s00247-007-0503-4
7. Vega RA, Opalak C, Harshbarger RJ, Fearon JA, Ritter AM, Collins JJ, Rhodes JL (2016) Hypophosphatemic rickets and craniosynostosis: a multicenter case series. J Neurosurg Pediatr 17(6): 694–700. https://doi.org/10.3171/2015.10.Peds15273
8. Fearon JA (2014) Evidence-based medicine: craniosynostosis. Plast Reconstr Surg 133(5):1261–1275. https://doi.org/10.1097/prs.0000000000000093
9. Willis FR, Beattie TJ (1997) Craniosynostosis in X-linked hypophosphataemic rickets. J Paediatr Child Health 33(1): 78–79
10. Rothenbuhler A, Fadel N, Debza Y, Bacchetta J, Diallo MT, Adamsbaum C, Linglart A, Di Rocco F (2018) High incidence of cranial synostosis and Chiari I malformation in children with X-linked hypophosphatemic rickets (XLHR). J Bone Miner Res 33:1–7. https://doi.org/10.1002/jbmr.3614

11. Song HR, Park JW, Cho DY, Yang JH, Yoon HR, Jung SC (2007) PHEX gene mutations and genotype-phenotype analysis of Korean patients with hypophosphatemic rickets. J Korean Med Sci 22(6): 981–986. https://doi.org/10.3346/jkms.2007.22.6.981
12. Roy WA, Iorio RJ, Meyer GA (1981) Craniosynostosis in vitamin D-resistant rickets. A mouse model. J Neurosurg 55(2):265–271. https://doi.org/10.3171/jns.1981.55.2.0265
13. Jaszczuk P, Rogers GF, Guzman R, Proctor MR (2016) X-linked rickets and sagittal craniosynostosis: three patients requiring operative cranial expansion: case series and literature review. Childs Nerv Syst 32(5):887–891. https://doi.org/10.1007/s00381-015-2934-9
14. Balek L, Gudernova I, Vesela I, Hampl M, Oralova V, Kunova Bosakova M, Varecha M, Nemec P, Hall T, Abbadessa G, Hatch N, Buchtova M, Krejci P (2017) ARQ 087 inhibits FGFR signaling and rescues aberrant cell proliferation and differentiation in experimental models of craniosynostoses and chondrodysplasias caused by activating mutations in FGFR1, FGFR2 and FGFR3. Bone 105:57–66. https://doi.org/10.1016/j.bone.2017.08.016
15. Carpenter TO, Whyte MP, Imel EA, Boot AM, Högler W, Linglart A, Padidela R, van't Hoff W, Mao M, Chen CY, Skrinar A, Kakkis E, San Martin J, Portale AA (2018) Burosumab therapy in children with X-linked hypophosphatemia. N Engl J Med 378(21):1987–1998. https://doi.org/10.1056/NEJMoa1714641
16. Saito T, Nishii Y, Yasuda T, Ito N, Suzuki H, Igarashi T, Fukumoto S, Fujita T (2009) Familial hypophosphatemic rickets caused by a large deletion in PHEX gene. Eur J Endocrinol 161(4):647–651. https://doi.org/10.1530/EJE-09-0261
17. Kinoshita Y, Saito T, Shimizu Y, Hori M, Taguchi M, Igarashi T, Fukumoto S, Fujita T (2012) Mutational analysis of patients with FGF23-related hypophosphatemic rickets. Eur J Endocrinol 167(2): 165–172. https://doi.org/10.1530/EJE-12-0071