Craniosynostosis as the Presenting Feature of X-linked Hypophosphatemic Rickets

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Craniosynostosis is the premature closure of cranial sutures. Primary, or congenital, craniosynostosis is often sporadic but may be associated with genetic or chromosomal abnormalities. Secondary craniosynostosis presents after gestation, and can occur in metabolic bone diseases, including rickets. We describe the first reported cases of primary craniosynostosis in 2 unrelated, term infants with X-linked hypophosphatemic rickets (XLH). The diagnosis of XLH in both patients was confirmed by genetic testing. At the time craniosynostosis was detected, the patient in the first case did not have any other clinical features of XLH. The second patient developed clinical findings of craniosynostosis, followed by rickets. These are the earliest reported cases of craniosynostosis in XLH and demonstrate that craniosynostosis may be a presenting feature of this disease.

BACKGROUND

X-linked hypophosphatemic rickets (XLH), the most common hereditary form of hypophosphatemic rickets, is caused by a loss of function mutation of the phosphate regulating endopeptidase homolog X-linked (PHEX) gene.1 Children affected by XLH typically have low serum phosphorus and inappropriately high urine phosphorus due to renal phosphorus wasting. Alkaline phosphatase is most often elevated, and vitamin D, serum calcium, and parathyroid hormone (PTH) levels are usually normal. Lower extremity bowing and impaired linear growth typically do not occur until the child is weight bearing. Because most children with hypophosphatemia are asymptomatic in infancy, those ultimately diagnosed with XLH typically do not come to the attention of medical providers until skeletal deformities and poor growth become apparent. The severity of patients’ clinical presentation is variable and can vary among family members with the same genetic mutation.1 Dental abnormalities, related to poor mineralization and dysplasia of dentin, and enthopathy due to abnormal calcification of tendons, joint capsules, and/or ligaments may also develop in XLH patients, although usually later in life.1,2 Craniosynostosis, the premature closure of cranial sutures, has been reported in patients with XLH. Craniosynostosis causes head shape deformity, and may, in a subset of patients, lead to increased intracranial pressure, ophthalmologic problems, and developmental delay. Primary or congenital craniosynostosis is typically diagnosed in infancy and may be isolated and sporadic, or, more rarely, is associated with specific genetic syndromes.3 Craniosynostosis secondary to underlying metabolic bone disease, including all forms of rickets, is less common and usually

abstract

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develops postnatally, much later than craniosynostosis caused by nonmetabolic disorders.4–7 We describe the first reported cases of primary craniosynostosis as the presenting feature of XLH diagnosed in early infancy.

CASE 1

A term female infant was born with an abnormally long cranium. At 3 months of age, she was diagnosed with scaphocephaly secondary to isolated sagittal synostosis, confirmed by a three-dimensional computerized tomography scan (Fig 1). Family history was notable for XLH due to a mutation in the PHEX gene (c.832G>A; p.Glu278Lys) in her mother, maternal grandmother, and maternal cousins. The mother was treated with phosphate and calcitriol and was otherwise healthy. Leading up to the patient’s diagnosis of craniosynostosis, she had normal growth and no features of rickets. At the age of 1 month, her serum phosphorus and calcium were normal. Results from repeat laboratory studies around 3 months of age showed low phosphorus and increased alkaline phosphatase, but normal serum calcium, PTH, 25-hydroxyvitamin D, and urine calcium. Urine phosphorus was 3 mg/dL (Table 1). The patient was referred for a pediatric endocrine evaluation, and based on the serum and urine laboratory test results in the setting of the family history, she was diagnosed with XLH. Treatment with phosphate and calcitriol was initiated. Results from subsequent genetic testing confirmed the XLH diagnosis, which identified the same PHEX mutation as found in her mother. According to our preferred institutional protocol, the patient had cranial vault remodeling at 5.5 months without complication (Fig 2). At 10 months of age, she was noted to have mild lower extremity bowing, which improved with continued treatment with phosphorous and calcitriol. At 2.5 years of age, the patient no longer had bowing of the lower extremities. Growth continued along the 30th to 45th percentiles, and at age 2.5 years, height z score was −0.47 SD.

CASE 2

An otherwise healthy term male infant with frontal bossing at birth was noted to have sagittal ridging at 3 months of age and protruding left occiput (or occipital “bullet deformity”) by 6 months of age. Skull radiographs showed diffuse calvarial thickening. A three-dimensional computerized tomography of the head revealed partial fusion of the sagittal suture with scaphocephaly and coarse trabecular thickening of the medullary cavity of the skull base, maxilla, and mandible. Linear growth, weight gain, development, and family history were normal. Laboratory evaluation showed low phosphorus, increased alkaline phosphatase, normal calcium, magnesium, 25- and 1,25-(di)hydroxyvitamin D, PTH, and renal function, but low tubular reabsorption of urine phosphorus, consistent with renal phosphate wasting (Table 1). A skeletal survey showed rickets changes. Results from genetic testing revealed a mutation in the PHEX gene (c.2198G>C; p.Cys733Ser), confirming XLH as the diagnosis. Phosphate and calcitriol supplementation was initiated and at 2 years of age the lower extremity bowing has nearly resolved. Current

![Primary sagittal synostosis in an infant (Case 1) with XLH. A, The entirely fused sagittal suture (arrow), anterior fontanelle, and open coronal (C) and metopic (M) sutures. B, The classic sagittal view of scaphocephaly and open coronal, lambdoid, (L) and squamosal sutures (S).](image)

<table>
<thead>
<tr>
<th>Table 1 Laboratory Values Before and at the Time of the Diagnosis of Craniosynostosis</th>
<th>Case 1</th>
<th>Case 2</th>
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<tbody>
<tr>
<td>Laboratory Values</td>
<td>Reference Ranges</td>
<td>1 Mo of Age</td>
</tr>
<tr>
<td>Phosphorus (mg/dL)</td>
<td>4.5–6.7</td>
<td>4.5</td>
</tr>
<tr>
<td>Calcium (mg/dL)</td>
<td>9.0–11.0</td>
<td>11.2</td>
</tr>
<tr>
<td>Alkaline phosphatase (U/L)</td>
<td>150–420</td>
<td>—</td>
</tr>
<tr>
<td>PTH (pg/mL)</td>
<td>12.0–88.0</td>
<td>20.2</td>
</tr>
<tr>
<td>25-hydroxy vitamin D (ng/mL)</td>
<td>30.0–100.0</td>
<td>—</td>
</tr>
<tr>
<td>FGF23 (RU/mL)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Urine calcium (mg/dL)</td>
<td>—</td>
<td>—</td>
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<tr>
<td>Urine phosphorus (mg/dL)</td>
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—, not applicable.
In a case series of 3 children younger than 1 year old has not been described with XLH and craniosynostosis, authors described 1 boy with a scaphocephalic head shape from birth, which suggested early development of craniosynostosis, but evaluation for and diagnosis of sagittal synostosis did not occur until he was 2 years old. In our 2 cases, we suggest expansion of the previously described time line of craniosynostosis development in children with XLH.

In a retrospective study, Seruya et al assessed the age of initial craniofacial evaluation in 211 children with craniosynostosis due to a variety of etiologies. In the entire cohort, the median age of presentation with craniosynostosis was 4.1 months. Patients with syndromes associated with craniosynostosis and those without syndromes presented at similar median ages of 4.0 to 4.1 months. In contrast, the 3 patients with XLH in that study presented at a much later median age (32.3 months). In one study of 59 children with different forms of rickets, the authors identified 16 children with craniosynostosis who were diagnosed at a median age of 45.6 months. In another study, the authors looked at 10 children with hypophosphatemic rickets, 5 of which had XLH, and described the evaluation of craniosynostosis in those with XLH ranging from 13 months to 5 years, with the median age of 24 months.

The development of craniosynostosis in general, and particularly in XLH, is not fully understood, and a variety of mechanisms have been proposed. Elevated concentrations of fibroblast growth factor 23 (FGF23) due to the loss of function mutation in the PHEX gene has been thought to lead to the deregulation of phosphate and vitamin D metabolism in patients with XLH. Interaction of FGF23 with FGF receptors 2 and 3 along cranial sutures has also been hypothesized as a mechanism of developing secondary craniosynostosis. Additionally, in mouse models, PHEX interacts with a matrix extracellular phosphoglycoprotein, which inhibits bone mineralization. Abnormal phosphate metabolism and inhibition of bone mineralization both have the potential to contribute to craniosynostosis. Vitamin D toxicity has previously also been suggested as a contributing factor in craniosynostosis development, and authors of 1 report described a 14-month old boy with XLH who developed craniosynostosis after 6 months of treatment with 1-α-cholecalciferol. The boy had symptoms of vitamin D toxicity, including anorexia, irritability, and failure to thrive, and was diagnosed with scaphocephaly and increased intracranial pressure. However, vitamin D is unlikely to be the only factor in development of craniosynostosis in children with XLH because many other cases of craniosynostosis develop in children without laboratory or clinical evidence of vitamin D toxicity.

Proposed mechanisms contributing to primary craniosynostosis include in utero fetal head constraint, prenatal exposures to valproic acid, maternal hyperthyroidism, and several genetic mutations. Mutations associated with syndromic craniosynostosis include twist homolog 1, fibroblast growth factor receptor 2, fibroblast growth factor receptor 3, and ephrin-B1. Mutations in twist homolog 1 are the cause of Saethre Chotzen syndrome, whereas fibroblast growth factor receptor mutations cause Pfeiffer and Crouzon syndromes, and mutations in ephrin-B1 cause craniofrontonasal dysplasia. These syndromes are often associated with bicoronal synostosis and midface anomalies, which were not found in our patients. Because genetic testing has not been shown to be helpful in cases of isolated sagittal suture synostosis, additional testing was not performed in our patients. In contrast, genetic testing is often performed for bicoronal or multisuture synostosis or craniosynostosis.
with other phenotypic features.\textsuperscript{17,18,20} Treatment, including surgery to allow for cranial expansion and normalization of head shape, and may be performed via strip craniectomy or open cranial vault remodeling, which is largely dependent on institutional preference.

To date, an association between congenital craniosynostosis and rickets has not been described. Previous reports on children with rickets suggest monitoring for skull changes once the rickets diagnosis is made,\textsuperscript{7,21} which often occurs after infancy. Our patients show that craniosynostosis can present early in life, before any other symptoms or treatment of rickets. We now suggest that screening for XLH and other forms of hypophosphatemic rickets could be included in the evaluation of primary or congenital craniosynostosis in patients with either a family history and/or clinical features of rickets. Initial tests may include serum alkaline phosphatase and phosphorous as well as urine phosphorous. These tests are a cost-effective method for the initial evaluation of primary craniosynostosis in patients with a family history of bone mineralization diseases or those with evidence of rickets. We also recommend surveillance for skull shape abnormalities by careful physical examination in all children at the time of diagnosis of XLH or other forms of rickets and repeated over time. We recommend that this monitoring is extended to infants and children who are at risk for familial forms of rickets.

**CONCLUSIONS**

Our patients presented with craniosynostosis as the initial manifestation of XLH. Initial signs of craniosynostosis were present at or soon after birth, in the absence of intruterine risk factors or prenatal exposures, and before any treatment of XLH was instituted. To our knowledge, these are the first reported cases of primary craniosynostosis in XLH and reveal that craniosynostosis may be a presenting feature of XLH. We recommend that the evaluation of primary craniosynostosis include consideration of XLH and other forms of hypophosphatemic rickets.

**ABBREVIATIONS**

FGF23: fibroblast growth factor 23

PHEX: phosphate regulating endopeptidase homolog X-linked

PTH: parathyroid hormone

XLH: X-linked hypophosphatemic rickets

**REFERENCES**


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