X-linked hypophosphatemic rickets with advanced bone age treated with aromatase inhibitor

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Summary

We present an adolescent with X-linked hypophosphatemic rickets (XLH) with bone age advancement and its response to aromatase inhibitors (AIs). A male with XLH, confirmed with a deletion on the PHEX gene, received regular treatment since the first year of life with average growth velocity and height. He had bone age compatible with chronological age until 13 when he had a bone age advancement and a decrease in the predicted final height thought to be due to initiation of oral isotretinoin, which has been previously reported. Then, anastrozole was initiated and maintained concomitant to the rickets treatment for 2 years with bone age stabilization. He had no adverse effects or worsening of bone health markers. As a result, he maintained his height gain and improved his final height Z score compared with the predicted final height at initiating anastrozole. In conclusion, although AIs was a reasonable strategy to stabilize bone age and minimize height impairment, careful monitoring is mandatory to understand its benefits and effects on XLH patients.

Learning points

• Although X-linked hypophosphatemic rickets patients have normal puberty, they can be affected by metabolic and environmental factors that may advance their bone age and impair the predicted final height, similar to the general population.
• Isotretinoin may accelerate skeletal maturation during puberty in an adolescent with X-linked hypophosphatemic rickets.
• Aromatase inhibitors showed to be a reasonable strategy to stabilize bone age and minimize height impairment in an adolescent with X-linked hypophosphatemic rickets.

Background

X-linked hypophosphatemic rickets (XLH) (OMIM 307800) is caused by inactivating mutations in the phosphate-regulating gene with homologies to endopeptidases on the X chromosome (PHEX) gene. It leads to a pathological increase in fibroblast growth hormone 23 (FGF23) levels with consequent suppression of calcitriol production, hyperphosphaturia, hypophosphatemia, and bone mineralization defect (1, 2, 3).

XLH phenotype includes disproportionate short stature, deformities in the lower limbs, such as genu varus, and reduced growth rate. However, these complications can be minimized to reach a greater final height with early diagnosis and treatment, which can be performed using sodium and potassium phosphate and calcitriol or burosumab, a monoclonal antibody against FGF23 (3, 4).
Although XLH patients have normal puberty with an average growth spurt, pubertal height gain, and growth plate estrogen-dependent maturation, they can be affected by metabolic and environmental factors that may advance their bone age and impair the predicted final height, similar to the general population. In order to delay growth plate closure and improve height gain, aromatase inhibitors (AIs), such as anastrozole, have been commonly used in the non-XLH pediatric population (5, 6, 7).

This report aims to present an adolescent with XLH and bone age advancement with reduced predicted adult height and its singular response to AI treatment.

**Case presentation**

Informed consent for a case report was obtained from the patient and their parents.

JPQ, a Brazilian male with non-consanguineous parents, was C-section delivered, early term, and appropriate for gestational age with no perinatal complications. Since his mother has hypophosphatemic rickets with many bone deformities, even with orthopedic surgeries, he was screened for rickets with a diagnosis confirmation when he was 1 year old. At the time, he presented failure to thrive and mild leg bowing without other symptoms like fractures or delay in motor skills. Moreover, his laboratory exams showed hypophosphatemia and hyperphosphatasemia with normal calcemia, parathormone, 25OHD, and renal function. Also, he presented low calciuria and hyperphosphaturia. In his knees x-ray, he had metaphyseal widening and fraying. Afterward, a panel for hypophosphatemic rickets confirmed the deletion of exons 18–20 from the \( \text{PHEX} \) gene.

During his follow-up at 4 years, he evolved with craniosynostosis, dolichocephaly, visual deficit, and nystagmus. In addition, the MRI confirmed Chiari anomaly type 1 and liquor sheath of optic nerves prominent within the orbits, except in the region of the optic canal. Also, CT of the orbits detected a slight narrowing of the distal optic canal and orbital fissures bilaterally, which explained his visual deficit.

After the diagnosis of rickets at 1 year of age, the patient was started on conventional treatment with sodium-potassium phosphate (50–60 mg/kg/day of elemental phosphate), calcitriol (20–30 ng/kg/day), and cholecalciferol (1000–2000 IU/day) and was being regularly treated until 14 years old. Then, he started using burosumab every 2 weeks (0.8mg/kg/dose) with average growth velocity and height \( Z \) score. His target height \( Z \) score was +0.08, but it was impacted by his mother’s short stature (height \( Z \) score: –2.88).

At age 10, he was prepubertal, presented an average height \( Z \) score (+0.08), and was overweight (Fig. 1). In addition, he had pectus carinatum, an olympic forehead, and genu valgus on the left leg. In his x-rays, he had a delayed bone age with a good prediction of final height (\( Z +0.44 \)), mild signs of rickets in his wrists and knees, and a slight deviation of the longitudinal axis of the thoracolumbar spine and kypholordosis. He started puberty at age 12 with Tanner and Marshall stage G2P2.

### Investigation

At 13 years of age, the patient was adherent to XLH treatment, had a healthy weight and average stature, and had a bone age compatible with chronological age, mild signs of rickets, and a predicted final height \( Z \) score of +0.2. At the time, he had a Tanner and Marshall stage G3P3. However, due to acne treatment, he used oral isotretinoin 0.5 mg/kg/day for 6 months, and right after that, the bone age advanced by 3 years with a decrease in the predicted final height (\( Z –1.58 \)) and a sustained Tanner and Marshall stage G3P3. During this time, he denied using other medication, hormones, or substances, and he denied musculoskeletal symptoms like arthralgia, myalgia, or back pain.

### Treatment

On account of that, isotretinoin was suspended, and anastrozole was initiated (1 mg/day) and maintained for 2 years with consequent bone age stabilization.

**Figure 1**

(A) At the age of 10, overweight patient with left genu valgus. (B) At the age of 17, patient with adequate weight and slight bilateral genu valgus. (C) Dolichocephaly.
Outcome and follow-up

During the anastrozole treatment and regular use of burosumab, he had no bone pain, muscle weakness, fractures, worsening of his bone deformities, or deterioration of his visual deficit and nystagmus. Also, there were no alterations in his lipid, glucose, hematocrit, testosterone, or liver enzyme profile. Therefore, he had no worsening of his bone markers like alkaline phosphatase. As a result, he maintained his height gain and improved his final height Z score (–0.99) above his mid-parental height at age 17 and 6 months. However, he persisted with skeletal changes, mainly dolichocephaly and slight bilateral genu valgus, without abnormalities in vertebral morphology (Fig. 1). His anthropometric and laboratory data are described in Table 1.

Discussion

XLH is a mineralization defect that leads to bone deformities, mainly in the lower limbs, with consequent disproportionate short stature. Delay in diagnosis and poor adherence to treatment lead to worsening body proportions with a decrease in growth velocity and final height (1, 2, 3, 4). The studied patient had an early diagnosis with regular treatment, which ensured a reasonable growth rate and good initial height prediction with minimization of orthopedic complications.

The height gain is determined by epiphyseal closure that occurs at different ages, depends on genetic predisposition and hormonal and environmental factors, and influences longitudinal bone growth. Humoral factors, like growth hormone, parathyroid hormone, cytokines, and estrogen, coordinate endochondral ossification through the balance between growth plate proliferation and senescence. Estrogen produced through the conversion of androgens by the aromatase enzyme has a dual effect on growth. It activates the growth hormone–insulin-like growth factor 1 (IGF-1) axis to promote growth acceleration and stimulates alpha- and beta-estrogen receptors to promote growth plate senescence with irreversible depletion of the number of chondrocytes in the resting zone. In XLH, puberty tends to have conventional onset and progression as in the general population with typical sex hormone production (1, 5, 6). The studied patient had a typical puberty onset at 12 years and average Tanner and Marshall stage progression, with normal testosterone and estrogen production.

However, environmental factors, such as endocrine disruptors and medications, may influence epiphyseal closure and impact final height prediction, even in XLH patients (6, 8). At 13.5 years, the studied patient had a skeletal maturation acceleration associated with isotretinoin, a vitamin A derivative that inhibits the function of the sebaceous glands and is used for acne treatment. Therefore, the bone age advancement could be influenced by his pubertal sexual hormones and a genetic predisposition to hormonal and environmental factors like isotretinoin.

Isotretinoin was associated with premature epiphyseal closure and growth plate abnormalities in numerous growth centers. Various durations and doses were related, ranging from the lowest dose of 0.5 mg/kg/day for a few months to 3.5 mg/kg/day for years. Retinoic acid may degrade the cartilage matrix component without evidence of apoptosis, advance skeletal maturation, and decrease the final height prediction (8).

One strategy to slow down bone age advancement and promote height increment is third-generation AIs, like

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Anthropometric and laboratory data of the patient.</th>
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<tr>
<td></td>
<td>Normal range</td>
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<tr>
<td>Height (Z)</td>
<td>+0.08</td>
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<tr>
<td>Predicted final height by bone age (Z)</td>
<td>+0.44</td>
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<tr>
<td>Serum calcium (mg/dL)</td>
<td>9.6</td>
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<tr>
<td>Serum phosphorus (mg/dL)</td>
<td>3.2</td>
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<tr>
<td>10–15 years</td>
<td>4.0–7.0</td>
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<tr>
<td>10–15 years</td>
<td>2.5–4.5</td>
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<tr>
<td>Total alkaline phosphatase (IU/L)</td>
<td>74–390</td>
</tr>
<tr>
<td>10–15 years</td>
<td>52–171</td>
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<tr>
<td>16–18 years</td>
<td>34.5</td>
</tr>
<tr>
<td>Parathormone (pg/mL)</td>
<td>11–67</td>
</tr>
<tr>
<td>16–18 years</td>
<td>34.5</td>
</tr>
<tr>
<td>25OHD (ng/mL)</td>
<td>&gt;30</td>
</tr>
<tr>
<td>10–15 years</td>
<td>&gt;95</td>
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<tr>
<td>Tubular reabsorption of phosphate (%)</td>
<td>&gt;95</td>
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25OHD: calcidiol.
anastrozole. It blocks androgen metabolism by reversibly binding to the aromatase catalytic site and reduces estrogen production, delays epiphyseal fusion, and extends the longitudinal growth period. Therefore, it allows a higher secretion of pituitary gonadotropins and testosterone, as the negative feedback loop is predominantly estrogen mediated in boys. However, the remanent estrogen production maintains growth through its joint action with IGF-1 in the growth plate’s resting and proliferative zones and does not promote senescence in the hypertrophic zone (7, 9, 10).

In the studied patient, anastrozole was started due to his bone age advancement and height prediction loss. Even though the concomitant use of recombinant human growth hormone with AIs has been positively associated with a gain in height prediction, it was not used for the studied patient due to the maintenance of a reasonable growth velocity (7). He tolerated the medication well and did not present any adverse effects. Furthermore, his total testosterone, gonadotropin, lipid, and glucose levels were in the reference range.

Despite beginning AI treatment with a bone age that was older than his chronological age, he experienced positive results as his bone age stabilized, and he achieved an increase in height gain (+0.59 SDS). Therefore, it is relevant to address the use of burosumab during the anastrozole treatment because it could have improved the growth velocity and influenced the patient’s final height (2).

A primary concern of using AIs is the impact of estrogen reduction on bone health since they promote bone reabsorption and reduce bone mass accrual and maintenance. However, previous studies showed a neutral effect of AIs on areal bone mineral density even though this was assessed by dual-energy x-ray absorptiometry without bone geometry or quality data. It is explained by elevated androgen bone-protective effects with the stimulation of periosteal bone expansion and the time-limited blockade. Moreover, in long-term follow-up data, an increase in vertebral irregularities and fractures rate was not associated with using AIs (9, 10).

The studied patient did not worsen musculoskeletal symptoms or bone markers during AI treatment. His adherence to the rickets treatment and using less potent AIs like anastrozole for a limited time may have reduced possible deleterious effects on bone health during the follow-up. However, careful prospective surveillance is needed to understand the effects in the long term on his elemental bone mineralization deficit caused by XLH.

In conclusion, AIs were a reasonable strategy to stabilize bone age and minimize height impairment in the studied adolescent with XLH. However, careful monitoring is mandatory, and more studies are necessary to understand the medication benefits and possible effects on XLH patients.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent
Written informed consent for publication of the submitted article and accompanying images was obtained from the patient and his parents.

Author contribution statement
J P Queiroz and G de Paula Colares Neto were responsible for collecting data from the patient and writing this article. S Lopes Lader assisted in the patient’s follow-up. C Marques Barroso and G de Paula Colares Neto were the endocrinologists in charge of the patient and his follow-up and were also responsible for the article’s review.

References


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