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Case report

Left Ventricular Hypertrophy in Patients with X-Linked Hypophosphataemia

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What is already known on this topic?
X-linked hypophosphataemia is a rare disorder with well-known mechanisms of low phosphorus levels but it does not clearly explain the cardiovascular involvement of these patients. Burosumab is a novel therapy of this entity, but it is not yet known whether its early onset can prevent complications.

What does this study add?
We report two patients with x-linked hypophosphataemia under burosumab therapy, one of them with more severe phenotype associating cardiac damage in the form of left ventricular hypertrophy. That patient had cardiac involvement while receiving conventional treatment, which has not been reversed after the start of burosumab therapy - although we have not found any worsening.

Abstract
X-linked hypophosphatemia (XLH) is a rare genetic disorder with x-linked dominant inheritance. The mutation on the PHEX gene increases fibroblast growth factor 23 (FGF23), causing loss of phosphorus at the proximal tubule. Most pediatric patients debut in the first two years with short stature and bow legs. Conventional treatment consists of oral supplements with phosphorus and calcitriol. Since 2018, burosumab is approved as a novel therapeutic option for XLH with promising results. The purpose of this study is to share our experience with two cases of XLH treated with burosumab. These patients presented with a broad phenotypical difference - the one with the most severe radiological phenotype developed left ventricular hypertrophy and left ventricular dysfunction with preserved ejection fraction. Treatment with burosumab was well-tolerated and was followed by radiological stability and a striking improvement in both patients' biochemistry and quality of life. The left ventricular hypertrophy was stabilized and left ventricular function normalized in the patient with cardiac involvement. In recent years many studies have been carried out to explain the role of FGF23 in cardiovascular damage, but the exact pathophysiological mechanisms are yet unclear. The most studied populations are patients with XLH or chronic kidney disease, as both associate high levels of FGF23. To date, cardiovascular involvement in XLH has been described in patients treated with conventional treatment, so it would be interesting to investigate if the early start of burosumab at the time of diagnosis of XLH prevents the occurrence of cardiovascular manifestations.
Key words: X-linked hypophosphataemia; FGF23; Arterial hypertension; Cardiovascular risk; Left ventricular hypertrophy; Burosumab

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Introduction

X-linked hypophosphataemia (XLH) is a dominant genetic disorder caused by mutations in the PHEX gene (Xp22.1) and constitutes one of the leading causes of inherited hypophosphataemia (prevalence of 4.8 per 100,000)[1]. The key physiopathological mechanism seems to be an increased production of fibroblast growth factor 23 (FGF23) by osteocytes and osteoblasts due to a loss of function in the PHEX gene[2]. FGF23 acts on proximal renal tubule binding to Klotho-FGF receptor complex inhibiting phosphate reabsorption and calcitriol production, leading to chronic hypophosphataemia[3].

Most pediatric patients with XLH manifest their first clinical symptoms in the first two years of life, presenting with disproportionate low height and bone deformities, especially at the lower limbs and craniosynostosis. Other complications such as enthesopathy, osteomalacia, dental abscesses or hearing loss often appear throughout these patients' lives[4]. There is a broad phenotypic spectrum even

among family members; consequently, a genotype-phenotype correlation is not well described[5]. The conventional treatment consists of oral administration of phosphorus and calcitriol but these supplementary therapies do not inhibit the action of the high levels of FGF23, and they do not stop the progression of the disease.
In 2018, burosumab, a human monoclonal IgG1 antibody neutralizing FGF23 was approved for the treatment of XLH[6]. Since then, burosumab has shown promising results with clinical improvement and quality of life for these patients[7]. We aim to share our experience with this novel treatment in two pediatric patients with different phenotypic patterns of XLH, focusing on cardiovascular complications in this population.

Case reports

The first case is a male patient diagnosed with XLH at 22 months old during the study of his low height and bowing limbs (Figure 1). Hypophosphataemia with hyperphosphaturia (Table 1) was detected, and mutations on the PHEX gene were examined by next-generation sequencing (NGS)[8] with detection of a mutation in hemizygosis. Therefore, he was initiated on conventional oral treatment. Poor biochemical and radiographic control persisted despite good therapeutic compliance, requiring hemiepiphysiodesis at 4 years old due to the significant deformity in the lower limbs. This led to walking disturbance and there was no improvement whatsoever. At the age of six, a first cardiovascular assessment with ambulatory blood pressure monitoring (ABPM), electrocardiogram (ECG), and echocardiography was carried out. The ABPM and ECG demonstrated no alterations, but the echocardiography revealed a concentric non-obstructive left ventricular hypertrophy (LVH) and associated subclinical left ventricular dysfunction parameters. Multiple criteria for definition of LVH in this patient were assessed (Table 1). The left ventricular ejection fraction was in normal ranges (>50%), but this parameter only assesses the systolic function and it is usually altered only in patients with clinically evident heart failure. To evaluate subclinical ventricular dysfunction, we used the Tei index, a parameter that includes both systolic and diastolic time intervals to assess the global cardiac dysfunction and detect early cardiac dysfunction in asymptomatic patients[9]. The Tei index is an easily performable, recordable and reproducible parameter that is influenced by age, sex, heart rate, and cardiac load conditions. A Tei index < 0.5 is the upper limit of normal (2 Zscore), and our patient presented with 0.57.
At that moment (2017), we decided to start burosumab (0.7 mg/kg every 15 days) as compassionate treatment. After 3 years (1.2 mg/kg every 15 days), the treatment has been well tolerated without significant side-effects. The values of serum phosphorus have increased to near normal values for his age. We have also noticed a slowed progression of the lower limbs' deformities with a significant improvement in quality of life (Figure 1A). Regarding the cardiovascular involvement, the dimensions of the left ventricle have remained stable, with a persistent LVH but with relatively reduced left ventricular mass index (Table 1). The left ventricular function has normalized (Tei index < 0.5).
The second case is a female patient diagnosed with XLH at 24 months old during the genu varus study. She had hypophosphataemia with hyperphosphaturia (Table 1), and we found a mutation in heterozygosis on the PHEX gene by NGS. She received conventional treatment, with persisting hypophosphataemia and worsening of the lower limbs' deformities (Figure 1B). Thus, she required hemiepiphysiodesis at 5.5 years-old, which was effective. The patient continued with hypophosphataemia and also very poor gastrointestinal tolerance to oral phosphorus. Therefore, we decided to start burosumab treatment (0.9 mg/kg every 15 days) at 9 years old (2019). ABPM, ECG and echocardiography were uneventful without signs of arterial hypertension, LVH, or left ventricular dysfunction. After 1.5 years, the treatment has been well tolerated. The hypophosphataemia has been improved, she maintains a good radiological progress and her intestinal symptoms have disappeared. The cardiovascular assessment remains normal.
Informed consent was obtained from both patients' parents.

Discussion

In this article, we present two patients with XLH with different phenotypic expression. According to our records the patient with the most severe radiological phenotype was diagnosed with LVH and left ventricular dysfunction by tissue Doppler echocardiography.
The definition of LVH is still controversial in children with multiple and variable existing criteria. The most commonly employed methods are adjusted for body surface area (BSA) or height, usually to an allometric power as the relationship between left ventricular mass (LVM) to height is not linear. Daniels et al. suggested the use of height$^{2.7}$ for indexing LVM based on studies relating LVM to lean body mass (LBM) in older children[10]. This boy fulfilled the LVH definitions recommended by current pediatric arterial hypertension guidelines[11]: left ventricular mass index (LVMI) > 51 g/m$^{2.7}$, LVM > 115 g/BSA and LVM >95th percentile for age[12]. Some authors raise the question of whether a higher cut-off (99th vs 95th percentile) should be used, and our patient also met this condition[13].
The utility of LVM/height$^{2.7}$ in children has been questioned due to the index variation in the lower age and lower height groups[14,15]. Thus, XLH patients usually present a low height for their age, and these criteria could lead to an overestimation of LVMI and LVH diagnosis in this population. Chinali et al. showed that the allometric power of 2.16 provides the best fit model[14]. This method provides normal reference values of LVMI, even for children under 140 cm of height, which is more appropriate for XLH patients. In particular, a LVMI greater than 45 g/m$^{2.16}$ would represent the 95th percentile across the whole pediatric age range independent of the sex and height to identify LVH, and our patient also met this criterion. Other LVH criteria assessed in this case were a LVM > 2.5 Zscore for BSA[16] and an interventricular septum diastolic diameter > 2.5 Zscore for BSA[17].
The normalization of the LVM to various functions of height, BSA, or body mass index (BMI) can alter the interpretation and classification of LVH in children. LVM varies in proportion to LBM but is usually expressed relative to height or BSA, each of which functions as a surrogate for LBM. Foster et al. provided normal percentiles of LVM for LBM[15], and our patient presented >97th percentile of LVM for LBM in the first echocardiographic control. Despite the existing controversy and the absence of definitive LVH criteria, particularly in low height populations, we provided data that the patient 1 met multiple criteria for LVH. Our patient 2 only fulfilled the LVH criteria of LVMI > 51g/m$^{2.7}$ and LVMI (g/m$^{2.7}$) > 95th percentile for age, reinforcing the need to use specific criteria for the correct assessment of LVH in this population.
XLH is actually associated with LVH and its relationship with FGF23 levels and arterial hypertension as causative mechanisms in this setting remain uncertain, as reflected by the controversial published literature. Takashi et al. did not observe LVH in 10 adults with XLH[18]. Pastor-Arroyo et al. studied the increased risk of cardiovascular disease in XLH mouse models (*PhexC733R*), which

showed increased FGF23 and PTH levels, hypophosphataemia, low 1,25(OH)2D levels, and low soluble Klotho, but not arterial hypertension, LVH or cardiac dysfunction[19]. Similar results were found in the study of Liu et al. in male Hyp mouse model of XLH[20]. Hernández-Frias et al. reported twenty-four pediatric patients with XLH and they observed LVH in 18%. They did not find correlation with FGF23 levels and only one case presented with associated arterial hypertension[21]. Accordingly, although our patient with LVH showed the most severe radiological phenotype of XLH, both cases presented high levels of FGF23 and normal ranges of blood pressure. Therefore, pathophysiological mechanisms different than increased FGF23 and arterial hypertension might be involved in the development of LVH in XLH patients.

On the other hand, recent evidence suggests a role of FGF23 in the development of cardiovascular involvement in XLH, particularly LVH and hypertension. Studies in animal models showed that FGF23 increases intracellular calcium levels, stimulating cardiac muscle contractility with subsequent LVH. The abnormal calcium deposition in the vascular tissue causing arterial hypertension and subsequent LVH in relation with increased FGF23 has also been reported[22,23]. Nehgme et al. studied thirteen patients with XLH with an average age of 13.5 years. They found LVH in 54% of cases, but they did not research the correlation with FGF23 levels. However, they proved that all patients with XLH had significantly higher diastolic blood pressure than the control group at the peak of exercise ergometry[24]. While the association of arterial hypertension with LVH was not assessed, these results suggest that XLH patients manifest certain vascular dysregulation as a substrate for the development of LVH. It should be noted that in pediatric patients (1-18 years), hypertension is defined as average clinic measured systolic blood pressure (SBP) or diastolic blood pressure (DBP) $\geq 95^{th}$ percentile (based on age, sex, and height percentiles). In recent years the American Academy of Paediatrics has updated the guidelines with new reference values for the pediatric population[11,25] , which should be used to avoid misclassification of hypertensive patients. The relationship between elevated levels of FGF23 and cardiovascular impairment, including LVH, has been widely investigated out of the XLH setting. It is known that chronic kidney disease (CKD) is associated with high levels of FGF23 and a deficiency of the co-receptor Klotho. The cardiovascular affectation seems to be directly caused by FGF23 by activating the intermediate molecule FGFR4, as myocytes do not express Klotho[26]. Mitsnefes et al. investigated the association of increased FGF23 and LVH in 587 pediatric patients with mild-moderate CKD. Interestingly, they showed a significant relationship between these two variables in spite of systolic blood pressure values[27].

Further studies would be necessary to clarify the exact mechanisms involved in developing cardiovascular manifestations in XLH. The LVH observed in one of our patients points out that serial cardiovascular assessment, including serial blood pressure determination, ECG and echocardiography, as well as the promotion of adequate control of cardiovascular risk factors would be recommended in this population. In our short-term experience, burosumab is an excellent therapeutic option for XLH in children, as it improves their quality of life and allows rapid biochemical stabilization without significant side effects. As we documented a stabilization in the LVH and a normalization of the left ventricular function after burosumab, a hypothetical role of this treatment in stabilizing XLH patients' cardiovascular manifestation could be argued. It seems not to have effects on reversing an already established LVH, but it could similarly slow the progression as it does with radiological manifestations. It would be interesting to study if the early administration of burosumab at the time of diagnosis of XLH would prevent cardiovascular complications in this population.

References

1. Haffner D, Emma F, Eastwood DM, et al. Clinical practice recommendations for the diagnosis and management of X-linked hypophosphataemia. Nat Rev Nephrol. 2019;15:435-55. Doi: 10.1038/s41581-019-0152-5.
2. Fukumoto S. FGF23-related hypophosphatemic rickets/osteomalacia: diagnosis and new treatment. J Mol Endocrinol. 2020:JME-20-0089.R2. doi: 10.1530/JME-20-0089.
3. Giralt M, Chocron S, Ferrer R, et al. Plasma intact fibroblast growth factor 23 level is a useful tool for diagnostic approach of renal hypophosphatemia. Pediatr Nephrol. 2021. Doi: 10.1007/s00467-020-04906-8.
4. Dahir K, Roberts MS, Krolczyk S, et al. X-Linked Hypophosphatemia: A New Era in Management. J Endocr Soc. 2020;4:bvaa151. Doi: 10.1210/jendso/bvaa151.
5. Scialla JJ, Wolf M. Roles of phosphate and fibroblast growth factor 23 in cardiovascular disease. Nat Rev Nephrol. 2014;10:268-78. Doi: 10.1038/nrneph.2014.49.
6. Padidela R, Cheung MS, Saraff V, et al. Clinical guidelines for burosumab in the treatment of XLH in children and adolescents: British paediatric and adolescent bone group recommendations. Endocr Connect. 2020;9:1051-6. Doi: 10.1530/EC-20-0291.
7. Martín Ramos S, Gil-Calvo M, Roldán V, et al. Positive Response to One-Year Treatment With Burosumab in Pediatric Patients With X-Linked Hypophosphatemia. Front Pediatr. 2020;18:48. Doi: 10.3389/fped.2020.00048.
8. Thiele S, Werner R, Stubbe A, et al. Validation of a next-generation sequencing (NGS) panel to improve the diagnosis of X-linked hypophosphataemia (XLH) and other genetic disorders of renal phosphate wasting. Eur J Endocrinol. 2020;183:497-504. doi: 10.1530/EJE-20-0275.
9. Cui W, Roberson DA. Left ventricular Tei index in children: comparison of tissue Doppler imaging, pulsed wave Doppler, and M-mode echocardiography normal values. J Am Soc Echocardiogr. 2006;19:1438-45. doi: 10.1016/j.echo.2006.06.006.
10. Daniels SR, Kimball TR, Morrison JA, et al. Effect of lean body mass, fat mass, blood pressure, and sexual maturation on left ventricular mass in children and adolescents. Statistical, biological, and clinical significance. Circulation. 1995;92:3249-54. doi: 10.1161/01.cir.92.11.3249.
11. Flynn JT, Kaelber DC, Baker-Smith CM, et al. SUBCOMMITTEE ON SCREENING AND MANAGEMENT OF HIGH BLOOD PRESSURE IN CHILDREN. Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents. Pediatrics. 2017;140:e20171904. doi: 10.1542/peds.2017-1904. Erratum in: Pediatrics. 2017; Erratum in: Pediatrics. 2018;142(3).
12. Khoury PR, Mitsnefes M, Daniels SR, et al. Age-specific reference intervals for indexed left ventricular mass in children. J Am Soc Echocardiogr. 2009;22:709-14. doi: 10.1016/j.echo.2009.03.003.
13. Gidding SS. Assessment of Left Ventricular Mass in Children and Adolescents: Current Status. J Pediatr. 2016;170:12-4. doi: 10.1016/j.jpeds.2015.12.042.

14. Chinali M, Emma F, Esposito C, et al. Left Ventricular Mass Indexing in Infants, Children, and Adolescents: A Simplified Approach for the Identification of Left Ventricular Hypertrophy in Clinical Practice. J Pediatr. 2016;170:193-8. doi: 10.1016/j.jpeds.2015.10.085.
15. Foster BJ, Khoury PR, Kimball TR, et al. New reference centiles for left ventricular mass relative to lean body mass in children. J Am Soc Echocardiogr. 2016;29:441–7.e2. doi: 10.1016/j.echo.2015.12.011.
16. Foster BJ, Mackie AS, Mitsnefes M, et al. A novel method of expressing left ventricular mass relative to body size in children. Circulation. 2008;117:2769-75. doi: 10.1161/CIRCULATIONAHA.107.741157.
17. Pettersen MD, Du W, Skeens ME, et al. Regression equations for calculation of z scores of cardiac structures in a large cohort of healthy infants, children, and adolescents: an echocardiographic study. J Am Soc Echocardiogr. 2008;21:922-34. doi: 10.1016/j.echo.2008.02.006.
18. Takashi Y, Kinoshita Y, Hori M, et al. Patients with FGF23-related hypophosphatemic rickets/osteomalacia do not present with left ventricular hypertrophy. Endocr Res. 2017;42:132-7. doi: 10.1080/07435800.2016.1242604.
19. Pastor-Arroyo EM, Gehring N, Krudewig C, et al. The elevation of circulating fibroblast growth factor 23 without kidney disease does not increase cardiovascular disease risk. Kidney Int. 2018;94:49-59. doi: 10.1016/j.kint.2018.02.017.
20. Liu ES, Thoonen R, Petit E, Yu B, Buys ES, Scherrer-Crosbie M, Demay MB. Increased Circulating FGF23 Does Not Lead to Cardiac Hypertrophy in the Male Hyp Mouse Model of XLH. Endocrinology. 2018;159:2165-72. doi: 10.1210/en.2018-00174.
21. Hernández-Frías O, Gil-Peña H, Pérez-Roldán JM, et al. Risk of cardiovascular involvement in pediatric patients with X-linked hypophosphatemia. Pediatr Nephrol. 2019;34:1077-86. doi: 10.1007/s00467-018-4180-3.
22. Faul C, Amaral AP, Oskouei B, et al. FGF23 induces left ventricular hypertrophy. J Clin Invest. 2011;121:4393-408. doi: 10.1172/JCI46122.
23. Okamoto Y, Fujita S, Morita H, et al. Association between circulating FGF23, α-Klotho, and left ventricular diastolic dysfunction among patients with preserved ejection fraction. Heart Vessels. 2016;31:66-73. doi: 10.1007/s00380-014-0581-9.
24. Nehgme R, Fahey JT, Smith C, et al. Cardiovascular abnormalities in patients with X-linked hypophosphatemia. J Clin Endocrinol Metab. 1997;82:2450-4. doi: 10.1210/jcem.82.8.4181.
25. Macumber I. Ambulatory Blood Pressure Monitoring in Children and Adolescents: a Review of Recent Literature and New Guidelines. Curr Hypertens Rep. 2017;19:96. doi: 10.1007/s11906-017-0791-5.
26. Haffner D, Leifheit-Nestler M. Extrarenal effects of FGF23. Pediatr Nephrol. 2017;32:753-65. doi: 10.1007/s00467-016-3505-3.
27. Mitsnefes MM, Betoko A, Schneider MF, et al. FGF23 and Left Ventricular Hypertrophy in Children with CKD. Clin J Am Soc Nephrol. 2018;13:45-52. doi: 10.2215/CJN.02110217.

Table 1. Evolution of clinical, biochemical and echocardiographic parameters of the patients at different stages of the disease.

VARIABLE	PATIENT 1			PATIENT 2		
	DEBUT	**BEFORE BUROSUMAB**	**LAST FOLLOW-UP**	**DEBUT**	**BEFORE BUROSUMAB**	**LAST FOLLOW-UP**
Age and anthropomorphic measures						
Age (yr)	1.75	6	9	2	9	10
Weight (kg), (SD)	14.2 (+1.27)	27.3 (+0.71)	35 (+0.1)	12 (-0.85)	28.8 (-0.42)	33 (-0.36)
Height (cm), (SD)	83.5 (-2.32)	111.7 (-1.83)	129 (-1.27)	79.7 (-2.99)	116.5 (-2.9)	124 (-2.42)
BSA (m^2, by Mosteller)	0.57	0.92	1.12	0.51	0.96	1.06
LBM (Kg, by Peters)	-	21	27.4	-	22.5	25.7
BMI (cm/m^2)	20.4	21.9	21	18.9	21.2	21.5
PHEX mutation	Hemizygosis c.670c>T(p.[Gln224*])			Heterozygosis c.1061c>T(p.Pro534Leu)		
Laboratory (reference values)						
Calcium (mg/dl)	9.2 (9.4-10.8)	9.6 (9.4-10.3)	9.2 (9.4-10.3)	9.9 (9.4-10.8)	10.2 (9.4-10.3)	9.8 (9.3-10.3)
Phosphate (mg/dl)	2.2 (4.5-6.5)	2.5 (3.6-5.8)	3.4 (3.6-2.8)	2.4 (4.5-6.5)	1.8 (3.6-5.8)	3.5 (3.6-5.8)
ALP (40-462 mg/dl)	539	576	313	486	397	307
PTH (15-85 pg/ml)	77	30.6	63.2	46.7	156.6	68
25-OH-vitamin D (21-100 ng/ml)	24,9	29.4	40.7	21.3	24.9	39
1,25-OH-D-Vitamin (16-56 pg/ml)	106	44	42	30	36	41
FGF23 c-terminal (<145 RU/ml)	>427	>427	>427	>427	>427	>427

TRP (>85 %)	70	54.4	86	80	30	98
Tmp/GFR (mg/100 ml)	1.556 (5.1±0.9)	1.674 (4.6±0.6)	3.311 (4.6±0.6)	2.032 (5.1±0.9)	0.976 (4.6±0.6)	2.973 4.6±0.6)
Ca/Cr (0.2 mg/mg)	0.15	0.08	0.18	0.06	0.04	0.09
Nephrocalcinosis	No			No		
Ambulatory blood pressure monitoring						
24h mean SBP percentile	-	p86	p89	-	p90	p89
24h mean DBP percentile	-	p70	p77	-	p89	p84
SBP load (%)	-	12	15	-	13	10
DBP load (%)	-	14	11	-	9	11
Nocturnal dipping	-	Yes	Yes	-	Yes	Yes
Echocardiography						
Diameter of IVS for BSA, mm (Zscore)	-	12 (3.44)	11.5 (2.89)	-	8 (1.46)	8.5 (1.57)
LVM (g)	-	115	126	-	60.3	72.5
LVMI > 51(g/$m^{2.7}$)		Yes	Yes	-	Yes	Yes
LVM (g)/BSA (**LVH>115 in boys and >95 in girls)**		125	112.5		62.8	71
LVM for BSA (Zscore)	-	3.65	2.75	-	-0.12	0.38
LVM/$m^{2.7}$ (percentile for age)	-	85.3 (>99th)	63.3 (>99th)	-	39.9 (95-99th)	40.5 (95-99th)
LVM/[($m^{2.16}$) + 0.09] (>45g/$m^{2.16}$=LVH)	-	84.5	69.1	-	43.3	43.1

LVM percentile for LBM	-	>97th	93rd	-	5th	10th
LV Tei index (>0.50=dysfunction)	-	0.57	0.42	-	0.35	0.41
LVEF (%) (<50%=dysfunction)	-	63	67	-	65	67

Table 1. Evolution of clinical, biochemical and echocardiographic parameters of the patients at different stages of the disease. For definition of LVH a total of 5 different criteria have been assessed. Abbreviations: yr (years); SD (standard deviation); BSA (body surface area); LBM (lean body mass); BMI (body mass index); ALP (alkaline phosphatase); PTH (parathyroid hormone); FGF23 (fibroblast growth factor 23); TRP (tubular reabsorption of phosphate); Tmp/GFR (maximal tubular phosphate reabsorption per 100 ml of filtrate); Ca/Cr (urine calcium/creatinine ratio); ABPM (ambulatory blood pressure monitoring); SBP (systolic blood pressure); DBP (diastolic blood pressure); IVS (interventricular septum); LVMI (left ventricular mass index); LVM (left ventricle mass); LV (left ventricle); LVEF (left ventricular ejection fraction).

Figure 1. Radiological evolution of the patients

Figure 1A. Evolution of patient 1, requiring hemiepiphysiodesis at 4 years-old for 19 months which was not effective, withdrawn after starting treatment with burosumab. Upper left panel (1.75 years); Upper right panel (4 years); Bottom left panel (6 years); Bottom right panel (8 years). Figure 1B. Evolution of patient 2, with less lower limb deformity with a correction after hemiepiphysiodesis at 5.5 years-old during 9 months. Upper left panel (2 years); Upper right panel (5 years); Bottom left panel (6 years); Bottom right panel (9 years).