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RESEARCH

Clinical features of Italian adult individuals with X-linked hypophosphatemia: a multicenter retrospective study

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Abstract

Objective: X-linked hypophosphatemia (XLH) is the most common congenital phosphate disorder affecting individuals throughout the lifespan. We investigated the skeletal burden, the cardiovascular involvement, the diagnostic performance and the therapeutic management in a cohort of Italian adults with XLH.

Design: Cross-sectional study involving 15 Italian tertiary centers.

Methods: Retrospective study.

Results: In total, 170 adults (110 females and 60 males), aged 44.6 ± 14.6 (19–83) years, were identified. i) Skeletal deformities were detected in 87.1% of individuals, fractures/pseudofractures in 44.7%, osteophytosis in 65.4% and enthesopathies in 57.6%. Dental disease affected 72.4% of individuals. The skeletal burden was heavier in males than in females. ii) Hypertension occurred in 14.7% of individuals and was associated with elevated plasma intact FGF23 levels; dyslipidemia, diabetes and cerebrovascular events occurred in very few individuals. iii) FGF23 levels were measured in 30.0% of individuals; they were >30 pg/mL (nv 23–95) in nearly all individuals but overtly elevated in 58.8%. Genetic analysis has been performed in 86.5% of the cohort, and *PHEX* mutations were identified in 95.2% of the individuals without evidence of genotype/phenotype correlation. iv) 44.2% of individuals were on conventional therapy, 32.5% were on burosumab, and 23.3% were untreated. Individuals having received diagnosis in the adulthood (n = 14) were neither medically nor surgically treated during their childhood.

Conclusion: The burden of XLH disease in adulthood is determined by skeletal manifestations and dental disease and may be more severe in males. Additionally, cardiometabolic impairment may not be common. The disease burden impacts most of the individuals, beyond those presenting the criteria for burosumab reimbursement.

Significance statement

Data from a consistent cohort of adults with XLH highlighted that skeletal and dental disease-related complications significantly affect XLH individuals during adulthood and aging. Skeletal features associated with aging occur earlier in adults with XLH, being more evident when untreated or poorly treated with conventional therapy. The disease burden impacts most of individuals, beyond those presenting the criteria for burosumab reimbursement. The study contributes in increasing awareness toward adult XLH individuals and provides data for implementing the disease management and the health policy planning.

Keywords: hypophosphatemia; X-linked osteomalacia; FGF23; adults; skeletal deformities

Introduction

X-linked hypophosphatemia (XLH) is the most common genetic cause of rickets/osteomalacia. It is caused by inactivating mutations of the phosphate-regulated endopeptidase homologous gene *PHEX* located on the chromosome X. These mutations are associated with inappropriate circulating fibroblast growth factor 23 (FGF23) levels, resulting in elevated urinary phosphate excretion, impaired conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D and hypophosphatemia (1).

Clinical symptoms and signs manifest in childhood. Children with XLH show rickets, progressive deformities of the lower limbs, and stunted growth (2). Complications from the disease or its treatment typically occur later in life and include osteoarthritis, enthesopathy (ligament, tendon or joint capsule calcification), dental disease, tertiary hyperparathyroidism, hearing impairment, and nephrocalcinosis (1). In adults, enthesopathies, osteoarthritis and pseudofractures may cause musculoskeletal pain that limit individuals' quality of life and reduce their functional capacity (3, 4, 5, 6). Almost all adult individuals with XLH complain of joint pain and stiffness, with walking difficulties and functional limitation (3).

Medical management includes conventional therapy with phosphate and active vitamin D (such as calcitriol or alfacalcidol), which is often unsatisfactory and associated with adverse effects, whereas burosumab, a

recombinant human IgG1 monoclonal antibody that neutralizes circulating FGF23, has recently become available. The Italian Medicines Agency (AIFA, Agenzia Italiana del Farmaco) approved reimbursement for burosumab for children since 2020 and for adults aged 18–65 years since March 2023. The availability of a targeted anti-FGF23 therapy has offered adult individuals with XLH the opportunity to improve their symptoms and quality of life, as recently reported also in an Italian series (7). In addition, the new therapeutic approach has led specialists to pay increased attention to both clinical skeletal and extra-skeletal manifestations of adults with XLH.

European and international panels of experts have recently developed guidelines for the management of individuals with XLH (8, 9, 10, 11); in adults with XLH, the following items have been identified as clues: i) clinical diagnosis of XLH by the identification of skeletal-related features; ii) biochemical diagnosis of XLH by determination of circulating FGF23; iii) genetic diagnosis of XLH on peripheral blood DNA; and iv) therapeutic management considering conventional therapy or burosumab.

The aims of the present study were to retrospectively evaluate the clinical aspects and management of adult XLH individuals referred to Italian third-level bone metabolism centers in order to i) characterize the clinical presentation of adult XLH individuals, ii) assess the burden of the disease in adults, iii) evaluate the diagnostic accuracy, and iv) assess the therapeutic options provided to XLH individuals in real life.

Subjects and methods

Study design

This is a cross-sectional retrospective study involving 15 Italian third level-bone metabolism centers. Specialists involved in the management of the present cohort of XLH individuals were endocrinologists (n = 22), nephrologists (n = 5), pediatricians (n = 2) and internists (n = 3).

The study followed STROBE recommendations for cohort study.

Patients

Inclusion criteria for the study were as follows: i) age ≥ 18 years; ii) clinical and/or genetic diagnosis of XLH. All individuals were invited to refer yearly for skeletal, dental and mineral evaluations. Their clinical, biochemical, radiological and genetic data were collected in a specific dataset from June 2023 to June 2025. Exclusion criteria included the following: i) absence of informed consent; ii) diagnosis of other FGF23-related hypophosphatemic diseases (such as autosomal dominant or recessive hypophosphatemic rickets, fibrous dysplasia and tumor-induced osteomalacia).

The occurrence of renal phosphate wasting and hypophosphatemia in the presence of signs and symptoms of osteomalacia suggested the clinical diagnosis of hypophosphatemic rickets. The biochemical diagnosis was confirmed by circulating FGF23 levels >30 pg/mL. Additionally, the identification of inactivating mutations or deletion of the *PHEX* gene established the genetic diagnosis of XLH.

All individuals gave their informed consent approved by the local ethical committees. The study complies with the Declaration of Helsinki.

Outcomes

The clinical features of interest included the following: i) bone-related features, such as a history of fractures or pseudofractures, and previous orthopedic surgery; ii) joint-related features, including osteoarthritis, osteophytes and enthesopathies, detected by clinical-based x-ray investigations; iii) dental-related features, such as a history of teeth abscesses or teeth loss: severe dental disease was defined as the occurrence of more than two spontaneous dental abscesses, or the loss of permanent teeth (complete or partial edentulism), or reported diagnosis of periodontitis; iv) cardiometabolic features reported in medical records, such as arterial blood hypertension, ongoing antihypertensive therapy, dyslipidemia, diabetes mellitus, previous major adverse cardiovascular events, defined as non-fatal stroke, non-fatal myocardial infarction or cardiovascular death; v) biochemical/hormone-related features, including measurement of circulating FGF23 levels and detection of *PHEX* gene variants; and vi) therapeutic approach throughout individuals' life.

Radiographic evaluation

X-ray of the spine or of skeletal segments was performed according to clinical judgment when patients reported pain. Pseudofractures, fractures (defined as the evolution of pseudofractures with the appearance of complete fractures, with the exclusion of traumatic or fragility fractures), enthesopathies and osteoarthritis were recorded. Kidney imaging, mainly ultrasound, for the detection of nephrolithiasis or nephrocalcinosis was available in most individuals (80%).

Circulating FGF23 assay

Circulating intact FGF23 was evaluated in the presence of hypophosphatemia with the commercially available assay (Diasorin, Liaison platform, Italy; reference range: 23–95 pg/mL; assay range: 5–5,000 pg/mL), recognizing the intact FGF23 molecule in EDTA plasma;

the assay kit is characterized by intra-assay coefficients of variation of 2.86 and 2.33% (12). Determinations were performed in the laboratory of each participating center.

Genetic analysis

Next-generation sequencing (NGS) was used to investigate gene sequence of the *PHEX* gene (ID ENSG00000102174). Multiplex ligation-dependent probe amplification (MLPA) analysis was performed on the DNA of the index cases that resulted negative by sequencing analysis to detect possible large monoallelic deletions or amplifications in the *PHEX* gene. Analyses were performed in the Laboratory of Molecular Genetics of each center.

Variants were classified according to the American College of Medical Genetics and Genomics and the Association for Molecular Pathology (ACMG-AMP) guidelines (13). Varsome and Franklin (Genoox, Israel) prediction tools were used to analyze the variants.

Statistical analysis

Data are presented as mean and standard deviation (SD), when passed the Shapiro–Wilk's normality test, or median and interquartile range (IQR). XLH individuals were divided into three age bands (18–30, 31–50 and ≥51 years) to estimate age-dependent changes in prevalence and analyzed by ANOVA; these age bands were adopted in order to reflect biologically and clinically distinct stages of XLH across adulthood, characterized by i) post-growth stabilization, closure of growth plates and achievement of peak bone mass (18–30 years), ii) progressive complication development (31–50 years) and iii) impact of progressive age (≥51 years). Chi-squared tests of independence were conducted to explore between-group differences for musculoskeletal, kidney, and dental features. A statistical significance level was set to 5% (P = 0.05). Analysis was performed by Jamovi, version 2.5.3, an open-source statistical software (The Jamovi project, 2025, https://www.jamovi.org).

Results

Clinical features in adult XLH individuals

Demographic features

One-hundred-seventy adult XLH individuals were enrolled, including 60 males, aged 45.0 ± 15.7 years, and 110 females, aged 44.3 ± 13.9 years. Of note, 28 individuals (16.5%) aged more than 60 years, ranging from 60 to 83 years. Median age at diagnosis was 6 years (IQR: 2.0–26.3); in particular, 101 individuals (59.4%) were diagnosed during infancy (<10 years), 18 (10.6%) during adolescence (10–18 years), and 54 (31.8%) in adulthood (≥18 years). Among individuals diagnosed with XLH in adulthood (mean age at diagnosis: 50.9 ± 17.6 years), 14 out of 54 (25.9%) had not received medical or surgical treatment during childhood or adolescence. Ninety-two XLH individuals (54.1%) had at least one affected parent.

XLH-associated clinical features

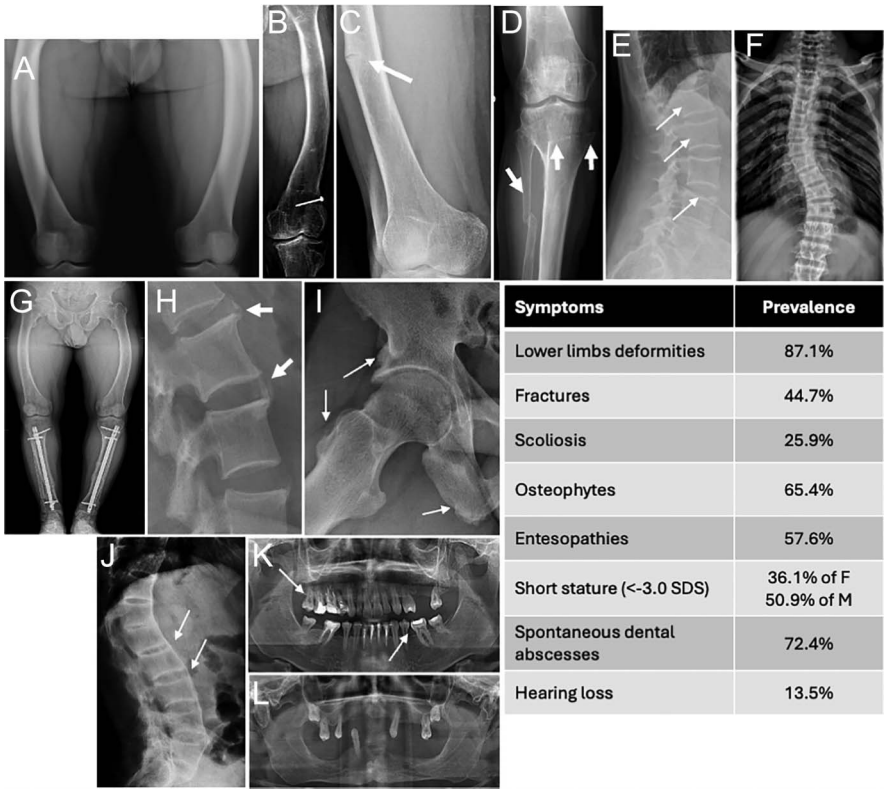
Skeletal deformities occurred in 148 individuals (87.1%); varus of the lower limbs was the most frequent deformity (n = 146, 85.9%), while scoliosis was detected in 44 individuals (25.9%). Because of skeletal deformities and loss of growth potential, females showed a median SDS height of −2.49 (IQR: −3.18, −1.98), while median height SDS was −3.14 (−3.94, −2.34) in males; height SDS was <−3.0 in 36.1% of females and 50.9% of males. Three individuals had previous diagnosis of Arnold-Chiari malformation and two of craniosynostosis. Fractures or pseudofractures, ranging from 1 to 10 lesions, were reported in 76 individuals (44.7%), primarily affecting the lower limbs, mainly the femur, tibia and fibula (Fig. 1).

Osteoarthritis with marked osteophytosis mainly affecting the spine was detected in 68 of 104 individuals with available radiological data (65.4%). Enthesopathies were described in 98 individuals (57.6%), most frequently affecting knees and scapulohumeral joints. Individuals aged >50 years (n = 58) had a higher prevalence of fractures/pseudofractures (62.1%), skeletal deformities (98.3%), osteoarthritis (93.2%) and enthesopathies (75.9%) than younger individuals (Table 1). More than two-thirds of the patients (72.4%) had severe dental disease, with a relevant prevalence since the young adulthood.

Kidney stones or nephrocalcinosis developed in 17 individuals (10.0%) with a mean age of 45.4 ± 14.1 years. Tertiary hyperparathyroidism occurred in 2.9% of the cohort (n = 5); all but one of these were aged over 60 years old at the time of the evaluation, and all were treated with subtotal parathyroidectomy due to hypercalcemia.

In the present cohort, 23 individuals (13.5%) reported a diagnosis of hypoacusia (mean age: 57.8 ± 14.7 years), although XLH individuals were not routinely screened for hearing impairment.

Individuals receiving diagnosis during childhood or adolescence showed higher prevalence of skeletal deformities and orthopedic surgeries compared to individuals who received a diagnosis in adulthood. Interestingly, untreated individuals during childhood who received diagnosis after 18 years showed higher prevalence of enthesopathies compared to patients diagnosed before the age of 10 and of 18 years (85.7 vs 42.4% vs 61.1%, respectively; P = 0.006) (Table 2).



Symptoms	Prevalence
Lower limbs deformities	87.1%
Fractures	44.7%
Scoliosis	25.9%
Osteophytes	65.4%
Entesopathies	57.6%
Short stature (<-3.0 SDS)	36.1% of F 50.9% of M
Spontaneous dental abscesses	72.4%
Hearing loss	13.5%

Figure 1

Prevalence of clinical skeletal-related features in the Italian cohort of adult XLH individuals. (A) Deformity of the bilateral proximal femurs with varism; (B) deformity of the distal femur with surgically partially corrected varism; (C) pseudofracture of the femur diaphysis (white arrow); (D) fracture of fibula and fracture of proximal tibia (white arrows); (E) lumbar vertebral deformities suggestive for osteomalacia; the white arrows indicate depression of the upper and lower vertebral body plates; (F) scoliosis; (G) short stature secondary to lower limb deformities due to bilateral varism and bilateral surgery for fracture/pseudofractures of tibia; (H) lumbar spine osteophytosis; (I) enthesopathies of coxofemoral joint (white arrows); (J) enthesopathies of spine anterior ligaments (white arrows); (K) multiple endocanalar treatment due to enlarged pulpar camera (white arrows); (L) severe edentulia secondary to recurrent dental abscesses. SDS, standard deviation score.

Cardiometabolic features

Median body mass index (BMI) was 26.7 kg/m^2 (IQR: 23.8, 29.9; *n* = 151); male individuals were heavier than females (27.6 kg/m^2; IQR: 25.4, 30.5 vs 26.1 kg/m^2; IQR: 23.1, 29.3; *P* = 0.034). Obesity, defined as having a BMI of 30 kg/m^2 or higher, affected 25.2% of individuals, while 44.4% of individuals were overweight (BMI between 25.0 and 29.9 kg/m^2). Two individuals were treated with sleeve gastrectomy and gastric bypass for obesity. Arterial blood hypertension and dyslipidemia were diagnosed in 14.7% (*n* = 25; mean age: 53.9 ± 10.7 years) and 11.2% of individuals (*n* = 19; mean age: 55.9 ± 12.0 years), respectively. Type 2 diabetes mellitus was diagnosed in one individual. Two individuals reported previous cerebrovascular events (one cerebral ischemic lesion due to patent foramen ovale and the second one due to ruptured cerebral aneurysm), while none reported clinically evident coronary diseases.

Comorbidities

Eighteen individuals (10.6%; 13 females and 5 males) reported autoimmune diseases, namely rheumatoid arthritis (*n* = 3), psoriatic arthritis (*n* = 1), Sjogren's syndrome (*n* = 1), thyroid diseases (*n* = 9),

Table 1 Phenotype according to age in XLH adult individuals. Data are presented as *n* (%).

		Age (years)			
Parameters	**Entire cohort**	**18–30**	**31–50**	**>50**	***P***
n	170	28	84	58	-
Female/male	110/60	18/10	55/29	37/21	0.978
Fractures/pseudofractures	76 (44.7)	11 (39.3)[§]	29 (34.5)[§]	36 (62.1)	0.004
Skeletal deformities, surgery	148 (87.1)	21 (75.0)[§]	70 (83.3)[§]	57 (98.3)	0.004
Osteoarthritis	68 (64.8)	0 (0)[§]	27 (57.4)[§]	41 (93.2)	<0.001
*n**		14	47	44	
Entesopathies	98 (57.6)	8 (28.6)[§,‡]	46 (54.8)[§]	44 (75.9)	<0.001
Dental disease	123 (72.4)	16 (57.1)	60 (71.4)	47 (81.0)	0.065
Hypertension	25 (14.7)	0 (0)[§]	9 (10.7)[§]	16 (27.6)	0.001
Kidney stones, nephrocalcinosis	17 (10)	1 (3.6)[†]	9 (10.7)[†]	7 (12.1)[†]	0.447

*Individuals with radiological data. [†]Symptomatic or asymptomatic, detected by ultrasound imaging. [‡]*P* < 0.05 versus individuals aged 31–50 years. [§]*P* < 0.05 versus individuals aged > 50 years.

Table 2 Phenotype according to age at diagnosis of XLH (*n* = 131); 40 patients treated with conventional therapy in infancy though the diagnosis of XLH was received in their adulthood, were excluded. Data are presented as *n* (%) or as mean ± SD.

	Age at XLH diagnosis (years)			
Parameters	**<10**	**10–17**	**≥18***	***P***
n	99	18	14	-
Females/males	61/38	10/8	10/4	0.654
Age (years)	39.8 ± 13.2‡,§	47.6 ± 14.5	50.9 ± 17.6	0.015
Fractures/pseudofractures	38 (38.4)	11 (61.1)	7 (50.0)	0.169
Skeletal deformities, surgery	87 (87.9)	15 (83.3)	9 (64.3)	0.051
Osteoarthritis	24 (49.0)	10 (76.9)	8 (66.7)	0.146
n†	49	13	12	
Enthesopathies	42 (42.4)§	11 (61.1)	12 (85.7)	0.006
Dental disease	70 (70.7)	13 (72.2)	8 (57.1)	0.566
Hypertension	17 (17.2)	4 (22.2)	2 (14.3)	0.825

*Individuals not medically or surgically treated in infancy. †Individuals with radiological data. ‡$P < 0.05$ versus individuals with diagnosis at age 10–17 years. §$P < 0.05$ versus individuals with diagnosis at age ≥18 years.

inflammatory bowel diseases (*n* = 1), multiple sclerosis (*n* = 1), vitiligo (*n* = 1) and vasculitis (Henoch–Schoenlein purpura, *n* = 1).

Gender difference

In the present cohort, the ratio female/male was 1.8. Males experienced a more severe phenotype than females, with a higher prevalence of fractures or pseudofractures (58.3% vs 37.3%, $P = 0.008$) and severe dental disease (85.0% vs 65.5%, $P = 0.006$). In postmenopausal women, skeletal deformities and osteophytosis were more common than in premenopausal women, while the prevalence of severe dental disease was comparable (Table 3).

Diagnostic outcomes

Circulating FGF23 levels

Plasma intact FGF23 levels were measured in 51 out of 170 individuals; the median level was 109 pg/mL (IQR: 67.7–171.4 pg/mL). FGF23 levels were higher than the upper limit of normal (ULN, 95.4 pg/mL) in 30 patients (58.8%); indeed, FGF23 levels were >30 pg/mL in all individuals except one harboring a large deletion of the *PHEX* gene.

Patients with plasma FGF23 levels in the normal range did not differ from those with FGF23 levels exceeding the ULN in sex, prevalence of fractures, skeletal deformities, osteoarthritis or enthesopathies (Supplementary Table 1 (see section on Supplementary materials given at the end of the article)). Dental disease occurred more frequently in individuals with FGF23 levels within the normal range (76.2% vs 43.3%, $P = 0.020$), while hypertension was more frequently registered in individuals with elevated FGF23 levels (>95 pg/mL, 4.8% vs 26.7%; $P = 0.043$).

Genetic analysis

Genetic analysis was performed in 147 patients (86.5%); mutations or deletions of the *PHEX* gene were detected in 95.2% of individuals. In two individuals, NGS sequencing failed in detecting gene variants; additional three patients

Table 3 Gender difference in clinical phenotype. Statistical comparisons were conducted between the groups of premenopausal women, postmenopausal women and men. Data are presented ass median (range) or as *n* (%).

	All females	**Premenopausal females**	**Postmenopausal females**	**Males**	***P***
n	110	85	25	60	-
Age (years)	44 (33–54)	40 (31–49)*,†	62 (57–69)*	42 (33–56)	<0.001
Family history of XLH, yes	54 (49.1)	42 (49.4)	12 (48.0)	38 (63.3)	0.179
Fractures/pseudofractures, yes	41 (37.3)	31 (36.5)*	10 (40.0)	35 (58.3)	0.029
Skeletal deformities or multiple orthopedic surgeries, yes	94 (85.5)	69 (81.2)†	25 (100.0)	54 (90.0)	0.022
Enthesopathies, yes	67 (60.9)	47 (55.3)	20 (80.0)	31 (51.7)	0.056
Severe dental disease, yes	72 (65.5)	55 (64.7)*	17 (68.0)	51 (85.0)	0.023
Osteophytosis, yes	42 (61.8)	27 (51.9)†	15 (93.8)	26 (70.3)	0.006
	n = 68‡	*n* = 52‡	*n* = 16‡	*n* = 37‡	

*$P < 0.05$ vs males. †Compared against postmenopausal females. ‡Individuals with radiological data.

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tested negative for both NGS and MLPA analysis. In two other individuals, the only detectable alterations were intronic variants classified as benign/likely benign. In 5 out of these 7 individuals in which genetic analysis did not identify any variants or identified benign variants, circulating FGF23 levels were found to be above 65 pg/mL, ranging from 65.2 to 533.4 pg/mL.

A detailed report of genetic variants was available for 121 patients. Among them, *PHEX* gene missense, nonsense or frameshift mutations were detected in 83 patients (68.6%), while intronic variants, potentially affecting splicing, were detected in 30 patients (24.8%). Large gene deletions detected by MLPA analysis were identified in 8 patients (6.6%). Results are presented in Supplemental Table 2 and Fig. 2A. Most abundant variants were in exons 15, 17, 18 and 22, encoding for aminoacidic domains of the PHEX protein that cluster in the same region (Fig. 2B). Notably, exon 17 contains the zinc-binding motif, which is a pentapeptide characteristic of zinc metalloproteases including the protein encoded by the *PHEX* gene, while exon 22 contains 3 out of 10 conserved cysteine residues that are characteristic of neutral endopeptidase family (14).

Of note, 85 patients harbored pathogenic or likely pathogenic variants or deletions. Twenty-three gene variants, detected in 29 individuals, were classified as novel mutations because they were not previously reported in ClinVar. Among these, six single nucleotide polymorphisms (SNPs) and four intronic variants were considered likely pathogenic according to Varsome and Franklin (Genoox). Of note, three patients from the same family harbored the same in-frame deletion in exon 9 (*PHEX* c.1020_1022del), classified as a variant of uncertain significance (VUS); other two patients harbored an intronic variant in intron 9 (c.1079+5G>A), classified as a VUS but considered likely pathogenic by prediction tools.

No significant differences in clinical features were observed among patients with missense variants (n = 32), nonsense variants (n = 33), deletions or duplications (n = 26) or intronic mutations (n = 28) (Table 4). However, XLH individuals carrying missense or nonsense mutations showed a statistically higher prevalence of positive family history.

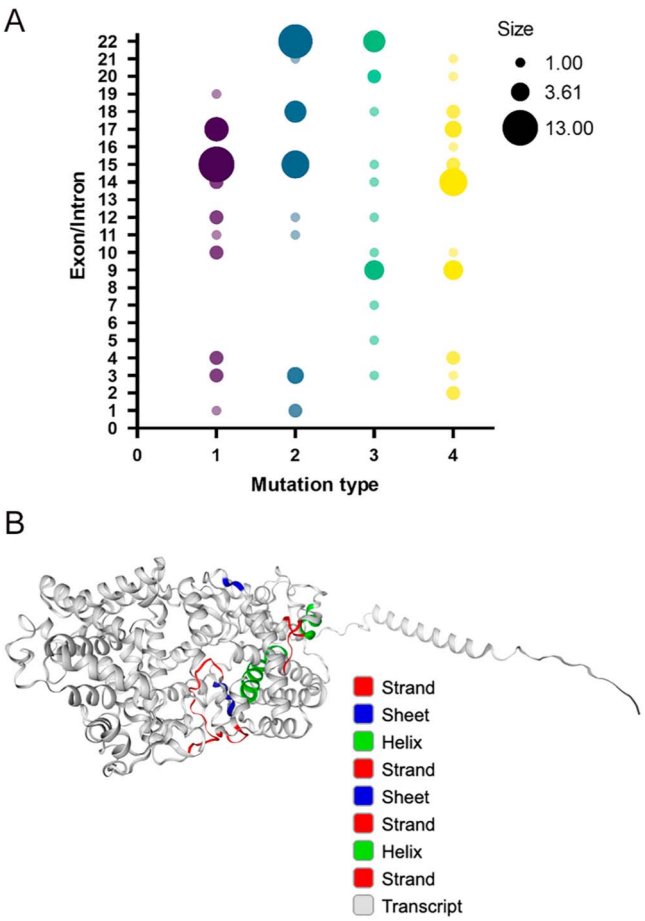

Figure 2

(A) Prevalence of gene variants according to type and exon/intron mapping in 112 XLH adult individuals. 1, missense mutations; 2, nonsense mutations; 3, deletions/duplications; 4, intronic mutations; size, number of individuals represented by each circle; individuals harboring deletions of more than 1 exon were not included. Data were analyzed by GraphPad 10.5.0. (B) Location of the aminoacidic changes induced by the most frequent gene mutations detected in the adult XLH cohort (exons 15, 17, 18 and 22; see Supplementary Table 2). The structure has been predicted by structure prediction of PHEX-201(749 aa) from AlphaFold v2.3.2 (Human protein atlas; https://www.proteinatlas.org/ENSG00000102174-PHEX).

Therapeutic management

At time of the present evaluation, 44.2% of the cohort (n = 72) was on conventional therapy with phosphate supplements and/or calcitriol; calcifediol was used in 15 individuals (8.8%), while two individuals were treated with paricalcitol due to concomitant renal secondary hyperparathyroidism with serum calcium levels at the upper limit of the normal range. Supplementation with cholecalciferol was provided in 50 individuals treated with conventional therapy or burosumab (29.4%). Duration and compliance with treatments were not available for all individuals.

Burosumab therapy was ongoing in 53 individuals (32.5%). Most individuals treated with burosumab had experienced previous fractures/pseudofractures compared with individuals on conventional therapy or untreated (77.4 vs 22.2% vs 34.2%, respectively; $P < 0.001$) (Table 5). Three individuals discontinued the treatment with burosumab because they did not meet anymore the AIFA reimbursement criteria for burosumab, two aged >65 years old and one individual beyond the age of epiphyseal fusion without at least one active

Table 4 Clinical features according to the different types of *PHEX* gene variants in 119 adult XLH individuals; two patients with benign/likely benign variants were not included. Data are presented as mean ± SD or as *n* (%).

Type of gene variants	Group 1 Missense	Group 2 Nonsense	Group 3 Deletions/duplications	Group 4 Intronic	*P*
n	32	33	26	28	
Age (years)	47.6 ± 12.3	44.7 ± 15.4	43.3 ± 16.7	44.9 ± 13.4	0.604
Sex (F/M)	22/10	20/13	16/10	16/12	0.818
Family history of XLH, yes	22 (68.8)*	25 (75.88)*,†	11 (42.3)	14 (50.0)	0.029
Fractures/pseudofractures, yes	16 (50.0)	14 (42.4)	13 (50.0)	13 (46.4)	0.921
Skeletal deformities or multiple orthopedic surgeries, yes	29 (90.6)	30 (90.9)	20 (76.9)	25 (89.3)	0.233
Entesopathies, yes	25 (78.1)	17 (51.5)	21 (80.8)	19 (67.9)	0.054
Severe dental disease, yes	26 (81.3)	24 (72.7)	18 (69.2)	23 (82.1)	0.589
Osteophytosis, yes	19 (76.0)	14 (56.0)	9 (50.0)	17 (77.3)	0.140
n‡	25	25	18	22	

F, female; M, male.
*$P < 0.05$ compared to Group 3. †$P < 0.05$ compared to Group 4. ‡Individuals with radiological data.

fracture/pseudofracture and skeletal pain. An additional individual stopped the treatment at the end of the first 3 months, because he did not experience pain relief nor improvement in his quality of life, although his phosphatemia was promptly normalized.

Thirty-eight individuals did not receive any specific treatment. Untreated individuals were older and with a higher prevalence of osteoarthritis and enthesopathies. Individuals on conventional therapy had a higher prevalence of nephrolithiasis compared to those on burosumab therapy or not taking any specific treatment, although the statistical significance was not reached (Table 5).

Discussion

The aim of this cross-sectional retrospective study, which included a cohort of 170 adult XLH individuals referred to 15 third-level centers in Italy, was to investigate the evolution of the disease in adult individuals and its treatment in the current Italian experience.

Our findings indicate that adults with XLH experience a significant burden in terms of skeletal features in disease progression across lifespan. Symptomatic and progressive skeletal deformities are reported as the most common manifestation (1, 15). Fractures/pseudofractures mainly involving lower limbs occurred in nearly half of patients, a prevalence similar to that reported in a recent multinational cohort (16). Osteoarthritis and osteophytosis affected about two-thirds of the cohort, while enthesopathies were detected in more than half of individuals. Although systematic clinical and radiological evaluations of the typical skeletal features were not common among the different institutions, the prevalence of osteoarthritis with marked osteophytosis in the Italian cohort was similar to that previously reported (16). Osteoarthritis was common in patients over 50 years old, almost absent in younger patients but increasing after 30 years of age, while the rate of enthesopathies (57.6%), which showed a significant increment with age, was higher than that observed in previous studies (15, 16). Enthesopathies were more prevalent in

Table 5 Phenotype according to current therapy in 163 XLH adult individuals; 6 patients waiting to start burosumab and 1 patient who discontinued burosumab after the epiphyseal fusion and under re-evaluation, were not included. Data are presented as mean ± SD, median (range) or as *n* (%).

Parameters	No therapy	Conventional therapy	Burosumab	*P*
n	38	72	53	-
Age (years)	53.3 ± 13.0†,*	42.3 ± 13.7	42.6 ± 14.3	<0.001
Females/Males	24/14	51/21	31/22	0.346
Fractures/pseudofractures	13 (34.2)*	16 (22.2)*	41 (77.4)	<0.001
Skeletal deformities	33 (86.8)	59 (81.9)	50 (94.3)	0.167
Osteoarthritis	30 (85.7)†,*	20 (54.1)	17 (53.1)	0.005
n‡	35	37	32	
Enthesopathies	33 (86.8)†,*	35 (48.6)	27 (50.9)	<0.001
Dental disease	30 (78.9)	48 (66.7)	38 (71.7)	0.399
Kidney stones/nephrocalcinosis	2 (5.3)	11 (15.3)	4 (7.5)	0.186
FGF23 levels (pg/mL)	67.2 (63.2–89.5)	120.0 (96.2–170.0)	127.0 (70.7–199.0)	0.410
n‡	3	17	27	

*$P < 0.05$ vs individuals treated with burosumab. †$P < 0.05$ vs individuals treated with conventional therapy. ‡Individuals with radiological data.

untreated individuals and in those diagnosed in adulthood who did not receive any medical or surgical treatment during childhood.

The burden of XLH disease was also determined by dental disorders, whose rate in the present cohort was comparable to that reported in other case series (16). Dental abscesses were commonly reported across all age groups, although no progressive increase with aging was detected.

Diseases with X-linked dominant inheritance are typically associated with a higher prevalence and a milder phenotype in females. In the present Italian cohort, males showed a more severe phenotype, with a higher prevalence of fractures/pseudofractures and severe dental disease, in contrast to previously reported series showing no gender-based phenotype differences in biochemical parameters and height z-scores in small series of young XLH individuals (17, 18). It is conceivable that, in adults, clinical phenotype may more clearly diverge according to gender. Furthermore, skewed X-inactivation, whereby the X chromosome harboring the gene variant is preferentially silenced, may be involved in determining a milder phenotype in females.

Kidney stones or nephrocalcinosis were reported in 10% of our cohort, a prevalence lower than those previously reported (19, 20). Likely, dose and duration of conventional treatment may be a main factor in explaining differences in the prevalence of kidney complications. However, the prevalence was likely underestimated due to the lack of systematic renal ultrasound screening.

Cardiovascular aspects have recently received attention in XLH patients, although conflicting data were reported. Several clinical studies have shown the presence of arterial hypertension and/or left ventricular hypertrophy (LVH) in patients with XLH (21, 22, 23, 24). The role of nephrocalcinosis, hyperparathyroidism and increased FGF23 levels in the development of hypertension and LVH has been suggested (21, 22, 24, 25). At variance, other studies did not detect an increased risk of developing LVH or hypertension (26, 27, 28). In the present cohort, hypertension was diagnosed in 14.6% of adults, while major cardiovascular events were uncommon, with only two individuals reporting previous cerebrovascular events and none with clinically evident coronary diseases. A higher prevalence of hypertension was detected in patients with higher circulating FGF23 levels; however, these data should be taken with caution considering the small sample size.

Some studies suggested that XLH individuals may be prone to metabolic disorders; in the general population, significant correlations have been reported between circulating FGF23, parathyroid hormone (PTH), 25-hydroxyvitamin D and phosphate levels and metabolic syndrome parameters (29, 30, 31, 32, 33, 34, 35, 36). An increased prevalence of overweight or obesity was observed in children with XLH (37).Moreover, glucose homeostasis was similar in adults with XLH compared to healthy controls, despite a high prevalence of overweight, obesity and excess fat mass involving 56% of patients (38), suggesting that metabolically healthy overweight and obesity predominate. In the present cohort, obesity and overweight, defined by using BMI, occurred in 25.2 and 44.4% of individuals, respectively. Indeed, BMI may overestimate adiposity in XLH patients due to their short stature and bone deformities (20). Italian XLH individuals were not systematically screened for impaired glucose metabolism, as well as dyslipidemia; however, only one patient had type 2 diabetes, while dyslipidemia was diagnosed in 11.2% of individuals. Taken together, although Italian adult XLH individuals showed a high prevalence of overweight and obesity, clinically evident cardiometabolic impairment did not appear to be frequent. However, given the young median age of the patients in this cohort, and the lack of an appropriate control population, definitive conclusions about cardiovascular involvement in individuals with XLH cannot be drawn.

Regarding other comorbidities, autoimmune diseases (AD) were reported in 10.6% of the cohort, with a higher prevalence in women (11.8%), as expected. This prevalence was similar to that estimated in the UK population (10.2%) (39) but higher than that reported in the US population (4.6%) (40); the prevalence of AD was of 1.6% in a female cohort of Italian early breast cancer patients (41), suggesting that the risk of developing AD requires monitoring in XLH individuals.

As regards diagnostic management, it emerged that FGF23 assay is not widely available in Italy, as National Healthcare System does not reimburse its measurement. Measurement of FGF23 may contribute to distinguishing FGF23-related hypophosphatemic osteomalacia from FGF23-unrelated forms and to suggesting the diagnosis of tumor-induced osteomalacia. FGF23 was determined in one-third of the individuals, and its circulating levels were within the normal range in a consistent proportion of XLH individuals. However, these values were likely inappropriately elevated for the degree of hypophosphatemia, as relying solely on the laboratory ULN cut-off for FGF23 would result in misdiagnosis in a large percentage of patients with XLH (42).

Genetic analysis of the *PHEX* gene is more accessible than FGF23 measurement as it has been performed in 87% of individuals. Collecting the NGS and MLPA results, the study provided a comprehensive and detailed report in a large cohort of Italian XLH adult individuals. Mutations or deletions of the *PHEX* gene were detected in 95.2% of analyzed individuals with clinical and biochemical diagnosis of XLH, although heterogeneity emerges. Missense, nonsense or frameshift *PHEX* gene mutations

were the most common alterations, detected in 68.6% of the cohort, but intronic mutations were detected in almost a quarter of the individuals. Most abundant *PHEX* variants were detected in exons 15, 17, 18 and 22, which encoded for aminoacidic domains of the PHEX protein clustering in the same region, whose function deserves further investigation. Mutations and deletions were widespread throughout all exons and introns, but exons 2, 6, 8, 13 and 16 were unaffected; the present findings were in line with previous reports (43, 44). Similarly to previous studies, the independent and multiple occurrences of the P534L/T and R747X mutations (14) indicated that these may represent *PHEX* codons or regions that are particularly prone to mutations. Of note, novel variants were detected in about 20% of individuals, and prediction tools suggested a likely pathogenic behavior in about half of cases. Our research expands the mutation spectrum of *PHEX* and highlights the importance of using multiple genetic testing methods, both NGS with inclusion of intronic regions and MLPA, to detect both single nucleotide polymorphisms and large deletions/duplications. Genetic analysis is useful to differentiate XLH from non-FGF23-related hypophosphatemic disorders and prevent inappropriate burosumab treatment, especially since many XLH patients have normal plasma FGF23 levels. Data regarding genotype–phenotype correlation are conflicting (43). Some studies reported differences in phenotype according to gender and position of the variant (45, 46, 47), whereas other recent studies (48, 49), similar to the present one, did not find any correlation with phenotype severity. Furthermore, variations in XLH phenotype have been observed among individuals within the same family, suggesting that modifier genes or environmental factors may contribute to clinical heterogeneity (45).

Most individuals were on ongoing treatment, mainly with conventional therapy. Burosumab treatment was provided to one-third of the individuals, who experienced fractures/pseudofractures, as the Italian regulatory agency AIFA reimburses burosumab only in adult XLH individuals who experienced at least one fracture/pseudofracture. Untreated individuals were older and with high prevalence of osteoarthritis and enthesopathies, while individuals treated with conventional therapy had more frequently experienced nephrolithiasis.

Overall, reports of affected parents of patients not being followed at any referral center, along with the substantial number of untreated individuals, highlight that XLH remains overlooked, undermanaged and undertreated in adulthood. It is crucial to consider that we should become more skilled at identifying enthesopathies and osteophytosis, to define the impact of burosumab treatment on the long-term complications of the disease.

The main strengths of our study are as follows: i) a specific focus on adult patients with XLH; ii) a real-world scenario that captures actual clinical management, treatment adherence and outcomes; and iii) a multicenter design involving several Italian referral centers, providing comprehensive and reliable data for the clinical picture of the XLH adult population in our country. Although most of the findings confirmed literature data, our cohort of Italian XLH individuals show some peculiarities, namely a consistent subset of individuals older than 60 years presenting a huge disease burden, mainly due to skeletal and joint deformities, and the observation that males are affected by a severe disease in terms of fractures/pseudofractures and dental complications. Moreover, the study provides a wide series of *PHEX* gene mutations, suggesting gene regions prone to mutations.

However, the study presents some limitations: i) this is a retrospective study; ii) XLH individuals have been managed before the availability of national and international recommendations; iii) the absence of standardized radiologic images and functional tests reduces the estimation of the burden of the disease and of its life-long progression; and iv) quality of life and hypophosphatemia-related fatigue were not investigated by specific questionnaires.

Conclusion

The current study collected data from a wide cohort of XLH individuals and could contribute to better understand the evolution of the disease and its treatment. Lower limb deformities and severe dental disease emerged as the major clinical features in these patients; in addition, enthesopathies and osteophytosis affected at least a half of the individuals at an early age, with enthesopathies being more prevalent in untreated patients. A higher prevalence of hypertension was observed in patients with higher FGF23 levels.

Bone specialists should implement their attention on the evaluation of the skeletal deformities, osteoarthritis, dental health and quality of life/fatigue in adult XLH patients.

Supplementary materials

This is linked to the online version of the paper at https://doi.org/10.1530/EC-25-0756.

Declaration of interest

GPA, MB, GIB, VC, SCa, EC, FC, PC, GG, LG, SG, SL, ML, AMP, FP, MP, SR, RMR, MOT, SV, SDV and MZ have no conflict of interest to declare. AP is a Senior Editor of *Endocrine Connections*. AP was not involved in the peer-review process for this manuscript, on which he is listed as an author. MLB received honoraria from Amgen, Bruno Farmaceutici, Calcilytix, Kyowa Kirin and UCB and received grants and/or speaker fees from Abiogen, Alexion, Amgen, Amolyt, Amorphical, Bruno Farmaceutici, CoGeDi, Echolight, Eli Lilly, EnteraBio, Gedeon Richter, Italfarmaco, Kyowa Kirin, Menarini, Monte Rosa, SPA, Takeda, Theramex and UCB; she is a consultant for Aboca, Alexion, Amolyt, Bruno Farmaceutici, Calcilytix, Echolight, Kyowa Kirin, Personal Genomics and UCB.

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Author contribution statement

SC acurated the data; performed visualization, investigation and formal analysis; and wrote the original draft of the manuscript. GIB, MB, EC, ML, GM, AMP and FP provided resources, performed investigation and wrote, reviewed and edited the manuscript. GPA, MLB, VC, FC, PC, CE-V, SG, LG, SL, LM, FP, AMP, MP, VR, SR, RMR and GV provided resources and wrote, reviewed and edited the manuscript. SDV, NEF, GG, MOT and MZ provided resources and performed investigation. SV provided resources. SC conceived the study, administered the project, curated the data, acquired funding and wrote the original draft of the manuscript.

Data availability

The data that support the findings of this study are openly available in zenodo at https://10.5281/zenodo.16723444.

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