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Disease-specific gait deviations in pediatric patients with X-linked hypophosphatemia

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ABSTRACT

Background: X-linked hypophosphatemia (XLH) represents the most common genetic form of rickets featuring profound hypophosphatemia with associated skeletal and non-skeletal manifestations. Early onset gait disturbances contribute strongly to the burden of disease. However, no study has comprehensively characterized naturally occurring gait deviations in pediatric patients with XLH.

Research questions: Can disease-specific gait deviations and potentially influencing factors be identified by gait analysis in non-surgically treated children with XLH?

Methods: Gait laboratory assessments of 12 pediatric patients with XLH without previous long bone surgery was retrospectively analyzed and compared to age-matched healthy controls. Radiologic and clinical parameters of XLH patients were correlated with kinematic gait variables and gait scores.

Results: Reduced external knee rotation and increased external hip orientation was ubiquitous in children with XLH. Increased lateral trunk lean, or "waddling gait", occurred in five children and was associated with varus knee deformities. Overall, children with XLH showed a reduced Gait Deviation Index (GDI) compared to controls. Radiologic and gait analysis revealed complex combined frontal and torsional deformity of the lower limbs as a common feature in XLH. Higher Body Mass Index (BMI) was associated with both lateral trunk lean and impaired GDI.

Significance: Gait analysis is feasible to quantify gait deviations and lower limb deformities in pediatric patients with XLH. Specific gait characteristics including internal knee rotation and external hip rotation are common among patients with XLH and contribute to impaired gait scores. Our data suggest the use of gait and deformity data assessment as outcome parameters in future observational and interventional studies. Standardized assessment might contribute to targeted treatments to improve life quality in XLH patients.

1. Background

X-linked hypophosphatemia (XLH) is caused by loss-of-function of phosphate-regulating gene with homology to endopeptidases on the X chromosome (PHEX). Due to dysregulation of Fibroblast-like growth factor 23 (FGF23), increased systemic levels induce chronic renal phosphate wasting and impaired activation of 25OH-Vitamin D (25-OHD) [1].

Common symptoms include rachitic deformities of the lower limbs and short stature as result of the chronic hypophosphatemia. Musculoskeletal pains, dental abscesses and fatigue further contribute to the substantially impaired quality of life in patients with XLH [2].

Conventional treatment consists of high-dosage administration of phosphate and active vitamin D to reduce rachitic changes and lower ALP levels. Radiographic monitoring mainly relies on the rickets severity score (RSS), a 10-point rating system for metaphyseal fraying and cupping of wrist and knee [3]. From 2019, the monoclonal FGF23-binding antibody is approved globally allowing to restore normal serum phosphate levels and to improve radiologic signs of rickets [4].

Bony deformities with bowing and maltorsion of long bones of the

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lower limbs are common features in XLH with multiple surgical treatment approaches [5–7]. The majority of patients with XLH report gait and joint problems as a burden of disease [8].

While gait abnormalities including increased lateral trunk lean, commonly referred as "waddling gait", are clinically well-known in XLH patients [9], concepts on the characteristics of XLH-specific gait pattern remain theoretical [5,7,10].

In contrast to other pediatric conditions with increased lateral trunk lean such as cerebral palsy, Legg–Calve-Perthes disease, arthrogryposis multiplex congenita or myelomeningocele [10], data on gait deviations in pediatric patients with XLH have not been comprehensively analyzed so far. Gait patterns of 9 mostly pre-operated adults with XLH have been described recently, but do not represent the naturally occurring gait deviations in the growing skeleton [11].

Thus, the aim of this study was to characterize and quantify naturally occurring gait abnormalities in children with XLH without prior surgical intervention. Further, this study aimed to identify radiographic, anthropometric or treatment associated risk factors associated with gait impairment.

2. Methods

A single center retrospective analysis of pediatric patients with XLH without previous surgical intervention was performed at the laboratory for gait and movement analysis, Orthopaedic Hospital Speising, Vienna. The study was approved by a local ethics committee (EK022020).

Inclusion criteria were genetically verified XLH and age under 16 years. Exclusion criteria were prior bony surgical procedures or prior guided growth.

Anthropometric data was retrieved at the time of gait analysis. Laboratory values and radiographs from maximum 6 months before or after gait analysis were included.

During the period from 2011 to 2019 gait analysis data of 20 children with XLH were available. 8 children (mean age 11.8 years) were excluded due to prior guided growth or osteotomy whereas 12 patients (m:f = 5:7) at a mean age of 8.8 years were included (Table 1). 10/12 patients received conventional treatment at the time of gait analysis with onset of medication at median 48.5 months of age, one patient was treated with antibody treatment, one patient was treatment naive.

Kinematic and kinetic gait analysis data were compared between the XLH group and an age matched control group of 18 healthy children with 36 lower limbs obtained from our gait laboratory database. The control group consisted of 12 girls and 6 boys, mean age 7.8 years (4–14 years, SD: 2.4 years). Subgroups were created for patients with valgus and varus lower limb axis malalignment.

Z-score calculations of body length, body proportions and BMI were based on recent Austrian reference data [12]. Treatment related data represents the treatment status at time of gait analysis. Alfacalcidol dosages were converted to calcitriol equivalents with a factor of 2:1 for a simplified analysis of treatment status.

Table 1
Basic characteristics and laboratory findings of included XLH patients.

	N	Mean	SD	Minimum	Maximum
Age (months)	12	105.6	46	49	177
Age at therapy onset (month)	7	30.6	30	3	80
Therapy duration (month)	7	68.1	55	8	149
Body height SDS	12	−2	0.8	−4.2	−1
BMI SDS	12	1.5	1.3	−0.4	3.5
RSS knee	11	1.9	0.7	1	3.5
Oral Phosphorous mg/kgBW/d	10	36.5	19	14.1	66.5
Oral Calcitriol ng/kgBW/d	10	25.6	9.9	10.5	44.4
Calcium (mmol/l)	12	2.4	0.1	2.3	2.5
Phosphate (mmol/l)	12	1	0.2	0.7	1.3
ALP (U/l)	11	395.6	65	309	503
25OH-D (nmol/l)	9	61.9	29	32.6	123
PTH (pg/mL)	12	47.8	22	12.7	73.1

SD = Standard deviation; SDS = Standard deviation score; BMI = Body mass index; RSS = Rickets Severity Score; kgBW = kg body weight; U = Units.

Full length anteroposterior (ap) radiographs (hip to ankle) of both lower limbs in standing position with a calibration ball were obtained as standard of care. Deformity analysis using the TraumaCad software (Brainlab AG, Munich, Germany) according to standard measurements [13,14] was performed by two independent, blinded examiners and mean values were used (Fig. S1). The mechanical axis deviation (MAD), neck shaft angle (NSA) and standard mechanical anteroposterior angles such as lateral proximal femoral angle (PFA), lateral distal femoral angle (LDFA), medial proximal tibial angle (MPTA) and lateral distal tibial angle (LDTA) were measured. RSS assessment was performed by two independent, blinded specialists [3]. For this study knee valgus deformity was defined as MAD > 10 mm and knee varus as medial MAD > 15 mm.

Gait analysis with a modified Cleveland model for movement of the lower extremity and a Plug in Gait model for movement of the upper extremity marker set was conducted using a Vicon motion capture system (Vicon, Oxford, United Kingdom) [15,16].

Patients walked the length of a 12-meter walkway barefoot at a self-selected speed. Kinematic data were calculated from a minimum of 10 gait cycles. Kinetic data from a minimum of five force plate strikes (force plates: AMTI Advanced Mechanical Technology Inc., Watertown, Massachusetts) per foot were collected. A custom Matlab script (The MathWorks, Natick, Massachusetts, Version 2019a) was used for graphing of data and comparisons between groups. The Gait Deviation Index (GDI) was calculated according to Schwartz and Rozumalski [17].

Standard kinematic and kinetic gait parameters of thorax, pelvis, hip, knee and ankle were assessed in sagittal, frontal and transverse plane. Intoeing was defined as mean internal foot progression during the single support phase. Increased lateral trunk lean was defined as increased medio-lateral range of motion of the thorax (norm + 2SD). External rotation of the hip and knee (mean values during stance phase) were defined as deviations exceeding two standard deviations of the control group values. The range of motion values (ROM) pertain to the whole gait cycle. According to Litrenta et al. a GDI of less than 70 was rated severe, 70–80 moderate and higher than 80 mild disease [18].

3. Statistics

Statistical analysis for comparison of gait parameters between XLH patients and age-matched controls included a Kolmogorov-Smirnov test for testing normal distribution, an independent- *t*-test (normal distributed) and Mann–Whitney *U* test (not normal distributed). For testing of waveforms statistical parametric mapping was used [19]. Statistics of gait parameters was calculated in Matlab and SPM in Python (Statistical Parametric Mapping. Retrieved from www.spm1d.org). Linear regression models were fitted using the least squares approach to quantify the strength of the relationship between BMI and GDI or lateral trunk lean, respectively. Assessment of strength was performed by R^2, statistical significance calculated using F-test. Pearson's or Spearman's correlations were calculated for normally and non-normally distributed parameters, respectively. Normal distribution was assessed by Shapiro-Wilk testing. The level of statistical significance was set at $p \leq 0.05$. Data was processed using Jamovi version 1.1.19 (The jamovi project, 2019. Retrieved from https://www.jamovi.org; R Core Team 2018. R: Retrieved from https://cran.r-project.org/).

4. Results

Children with XLH show impaired gait with increased frontal trunk movement, torsional abnormalities of the lower limb and decreased sagittal range of motion of the ankle and knee. Most patients showed Alkaline Phosphatase (ALP), Parathyroid hormone (PTH) and Calcium/Creatinine ratio values within the upper normal range (Table 1). There

Table 2
Gait Analysis Table.

	XLH, ° (n = 24 limbs)				Control, ° (n = 36 limbs)				
	Mean	SD	Min	Max	Mean	SD	Min	Max	P Value
Walking Speed normalized	0.461	0.093	0.299	0.576	0.497	0.0543	0.408	0.596	0.181
Step Width (m)	0.089	0.026	0.053	0.135	0.074	0.017	0.038	0.115	**0.007**
Step Length normalized	0.848	0.119	0.854	0.551	0.884	0.0765	0.710	1.012	0.148
Cadence normalized	0.540	0.056	0.416	0.616	0.561	0.031	0.511	0.621	0.913
Pelvis range of motion (ant./post; deg)	3.7	1.4	1.5	6.7	3.1	0.6	1.9	4.4	**0.022**
Pelvis range of motion (up/down;deg)	6.5	2.0	3.2	9.9	8.6	2.1	4.6	12.0	**0.000**
Hip sagittal range of motion (ext/flex; deg)	42.5	5.3	33.1	51.6	44.2	6.2	33.8	57.5	0.297
Knee sagittal range of motion (ext/flex; deg)	60.4	6.5	48.0	74.5	63.8	5.4	54.9	76.3	**0.032**
Ankle sagittal range of motion (df/pf; deg)	24.5	3.5	19.2	31.0	32.8	4.4	25.4	39.8	< **0.001**
Hip transversal. mean value stance phase (ext/int; deg)	−9.8	4.2	−17.7	0.1	3.1	5.4	−7.7	17.4	< **0.001**
Knee transversal. mean value stance phase (ext/int, deg)	5.8	10.1	−17.1	23.2	−19.3	8.6	−44.8	−0.9	< **0.001**
Foot progression angle mean value single support phase (ext/int, deg)	−1.4	6.7	−14.8	12.6	−7.9	5.2	−18.3	3.5	< **0.001**
Knee frontal. mean value stance phase (varus/valgus, deg)	3.7	11.8	−14.6	28.9	−0.6	2.2	−4.2	4.1	0.970
Lateral Trunk Lean frontal range of motion (deg)	6.3	4.0	2.1	15.8	2.9	1.3	1.00	6.1	< **0.001**
Gait Deviation Index	84.8	12.6	62.1	104.4	100	–	–	–	< **0.001**

*XLH = X-linked hypophosphatemia. SD = standard deviation. Min = minimum. Max = maximum. deg = . degrees.
The p values are for comparison of study population and control group data.
Note: In the sagittal plane. positive values = anterior (ant)/dorsiflexion (df)/extension (ext) and negative values = posterior (post)/plantarflexion (pf)/flexion (flex). In the transverse plane. positive values = internal rotation and negative values = internal rotation. In the frontal plane. positive values = adduction/up and negative values = abduction/down.

were no cases of profound hyperparathyroidism or Vitamin D deficiency.

Torsional abnormalities of the lower limb were observed in all patients during gait: The most severe abnormalities were found concerning the transverse plane (rotation/torsion) (Table 2, Fig. 1). Intoeing (internal foot progression) was observed in 8 feet (5 children). An external knee rotation less than 2.1° was a constant finding in all examined XLH patients and knee rotation values were significantly reduced in comparison to healthy controls ($p < 0.001$, Table 2, Fig. 1). The hip rotation was orientated externally compared to the control group ($p < 0.001$). 19 hips (11 children) exceeded 7.7° of external rotation.

Lateral trunk lean was significantly increased in XLH patients as compared to age-matched controls ($p < 0.001$, Table 2, Fig. 2**A**). "Waddling gait" as defined as frontal thorax ROM > 5.5° was observed in 5 patients. XLH patients with varus knee deformity revealed an increased lateral trunk lean correlating positively with medialization of the mechanical axis (varus knee deformity) (Spearman's rho = 0.4; $p = 0.4$, Fig. 2**B** + **C**; Table 3). No correlations with mechanical (mLPFA) or anatomic (NSA) proximal femoral deformity (mLPFA Pearson's r = -0.4, $p = 0.08$; NSA r = -0.2, $p = 0.3$) were found. Lateral trunk lean ROM was strongly associated with BMI Z-scores (Fig. 2**D**: $R^2 = 0.74$, $p < 0.001$. Covariate estimate BMI Z-Score: 2.7, SE 0.4, $p < 0.001$).

The XLH group showed overall abducted hip and reduced frontal pelvis range of motion through the whole gait cycle (Fig. S2, Table 2). The patients with varus malalignment of the lower limbs had increased hip abduction, slightly reduced frontal pelvis motion but increased lateral trunk lean (Fig. S3). The XLH patients with valgus malalignment of the lower limb had normal hip abduction, slightly reduced frontal pelvis motion and a normal lateral trunk movement (Fig. S3).

Extension and flexion (sagittal ROM) of the knee and the ankle was significantly impaired compared to healthy controls (knee: $p = 0.03$; ankle: $p < 0.001$, Table 2, Fig. S2). 12 ankles in 6 children showed decreased sagittal ankle ROM (less than 24°). The frontal knee measurements (gait analysis) showed varus and valgus deviations correlating with the radiographic findings (MAD) (r = -0.91, $p < 0.001$). Normalized walking speed and step length was not significantly decreased compared to the control group (Walking speed $p = 0.18$; step length $p = 0.15$; Table 2).

Reduced sagittal knee power and reduced knee extension moment was observed during loading response (Fig. S4). The frontal valgus knee moment was severely increased in the XLH group with varus knee deformity (Fig. S5).

Radiographic outcome (n = 12 children, 24 limbs) showed a mean mechanical axis deviation of - 10.3 mm (60 mm medial to 43 mm lateral) (Table 3). Knee valgus deformity (MAD > 10 mm) occurred in 7 of 24 limbs, knee varus (medial MAD > 15 mm) in 11 legs. 18 of 24 hips had a mechanical proximal femoral varus deformity (PFA > 90°). RSS was performed for all available lower limb and wrist radiographs performed +/- 6 months to gait analysis. Mean lower limb RSS (n = 21, 1.80 +/-0.73) and wrist RSS (n = 12, 2.0 + /- 1.45) revealed rachitic phenotypes in all examined patients.

Gait Deviation Index (GDI) as a global gait score showed a significantly reduced gait quality in children with XLH ($p < 0.001$, Table 2). Linear regression modelling indicated a strong correlation of GDI scores with BMI Z-scores and ALP as covariates (Fig. 2**E**; $R^2 = 0.77$, $p < 0.001$. Covariate estimates: BMI Z-Score: -7.6, SE 1.2, $p < 0.001$; ALP: -0.1, SE 0.02; $p < 0.001$). Age, body height Z-scores or body proportions did not reveal significant effects on this model.

5. Discussion

Gait abnormalities are a major cause of impaired QoL in patients with XLH [8]. While progressive mobility impairment is affecting most patients with XLH scientific characterization has mostly been limited to clinical descriptions, patient-reported outcomes or plain radiographic scorings.

This study showed disease specific radiographic and gait deviations leading to abnormal gait. Factors influencing gait quality such as lower limb deformity parameters and metabolic parameters were identified.

Since decades, short stature, long bone deformities and severe "waddling gait" are constantly reported as main clinical features in patients with vitamin-D resistant rickets [7,9,20]. In this study we refer to the poorly defined term "waddling gait" as "increased lateral trunk lean" to outline the underlying mechanical pathophysiology. Increased lateral trunk lean occurs in multiple orthopedic pathologies with different underlying pathomechanisms [10]. In patients with XLH, a decrease of gluteal muscle strength due to changed lever arm as a result of varus deformity of the proximal femur has been discussed as cause for the waddling gait pattern [5,20]. Other authors have hypothesized that "waddling gait" is influenced by the correction of knee varus deformity

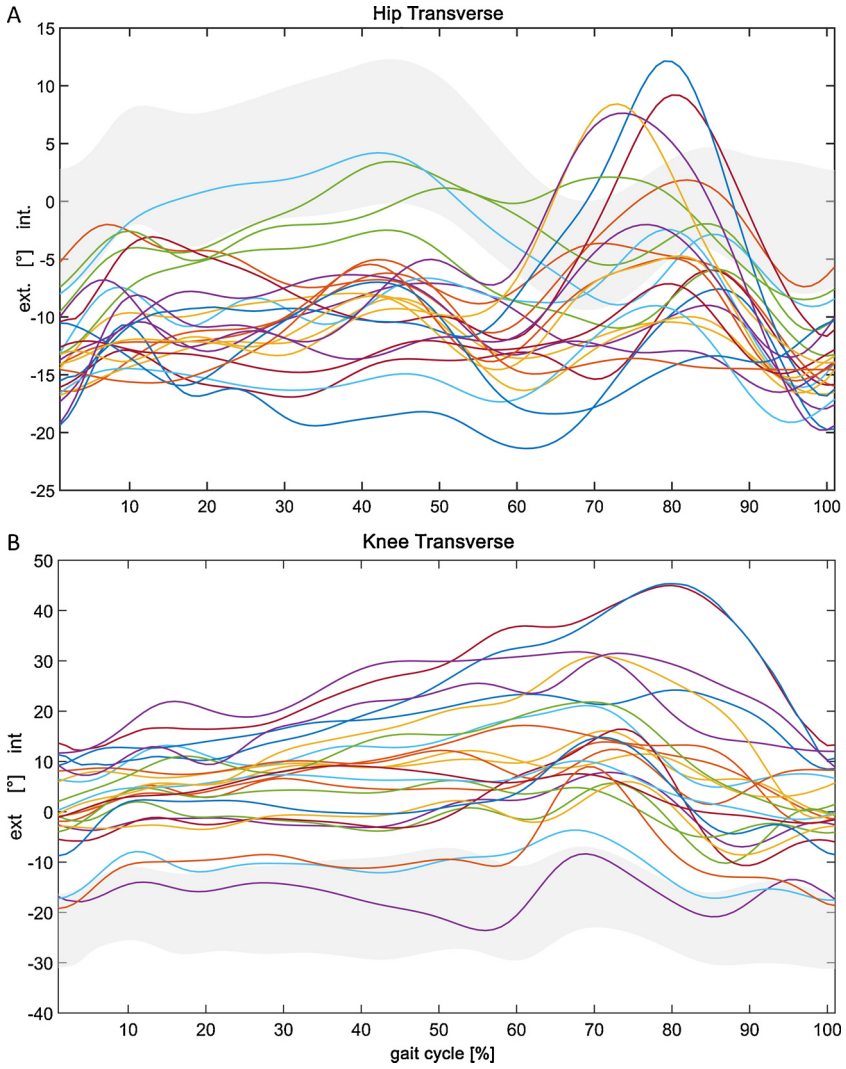

Fig. 1. Gait analysis - hip (1A) and knee rotation (1B). Colored lines indicate the mean hip or knee rotation of each limb of XLH patients (n = 24 legs), gray bands indicate the region within 1 SD of mean in the control group. External hip rotation (Ext) (negative values) and internal rotation (Int) (positive values) during the whole gait cycle. Increased external hip rotation was observed in nearly all limbs (Fig. 1A). Internal knee rotation (tibial rotation) (Int) (positive values) and external rotation (Ext) (negative values) during the whole gait cycle. Only one leg showed normal knee rotation during the whole gait cycle (Fig. 1B).

in patients with XLH [7] and that increased lateral trunk influences hip and knee kinetics [10]. However, none of these studies have used the combination of radiographic deformity analysis and gait analysis to comprehensively study increased lateral trunk lean and to prove their hypotheses. Our data supports the causative role of knee deformity as measured by MAD which correlated significantly with increased lateral trunk lean. In contrast to previous assumptions, proximal femoral deformity was not associated with this gait pattern in children and adolescents without previous surgery.

We conclude that increased lateral trunk lean “waddling gait” is the main compensation mechanism seen in XLH patients with varus limb alignment. The increased lateral trunk lean with normal frontal hip motion may compensate the main kinetic finding of increased valgus knee moment in varus knee deformities. However, the effectiveness of this potential compensation mechanism cannot be verified with our study design and study group size.

We observed decreased ankle ROM (dorsiflexion/plantarflexion) which is in accordance with the subjective feeling of joint stiffness as reported by a majority of children and adults with XLH [8]. While this common symptom in XLH may reflect typical features such as soft tissue mineralization, pain and axial deviations, decreased gait velocity could further contribute to impaired ROM values in our study.

Global gait scoring by GDI was feasible in all included XLH patients and showed a wide range of severity in gait deviations compared to other pediatric disease populations [18,21–23] (Table S1). This difference in gait affection might be both attributable to different pathomechanisms but also to varying age-distributions which impede a detailed comparison of GDI scores.

The occurrence rate of orthopedic problems in well-treated patients with XLH has been discussed in literature [9]. In this XLH cohort, we found only 6 of 24 limbs with normal frontal axis in this series while the majority of limbs had both varus knee deformities and torsional deformities. These complex skeletal deviations occurred on multiple levels leading to pathologic joint angles in the ankle, knee and hip. Bony deformity is a frequent indication for surgical intervention in patients with XLH [5–7]. Guided growth represents a minimal invasive surgical option to correct varus and valgus lower limb deformities in children with XLH and other skeletal conditions [5,7,24]. However, guided growth concepts are more challenging to use in patients with XLH due to complex deformities and impaired growth velocities as reflected by higher complication rates in this population [25]. Thus, XLH management should target an optimized conservative treatment to prevent bony deformity, to identify functional impairments for targeted therapies and therefore to reduce the number of surgical interventions

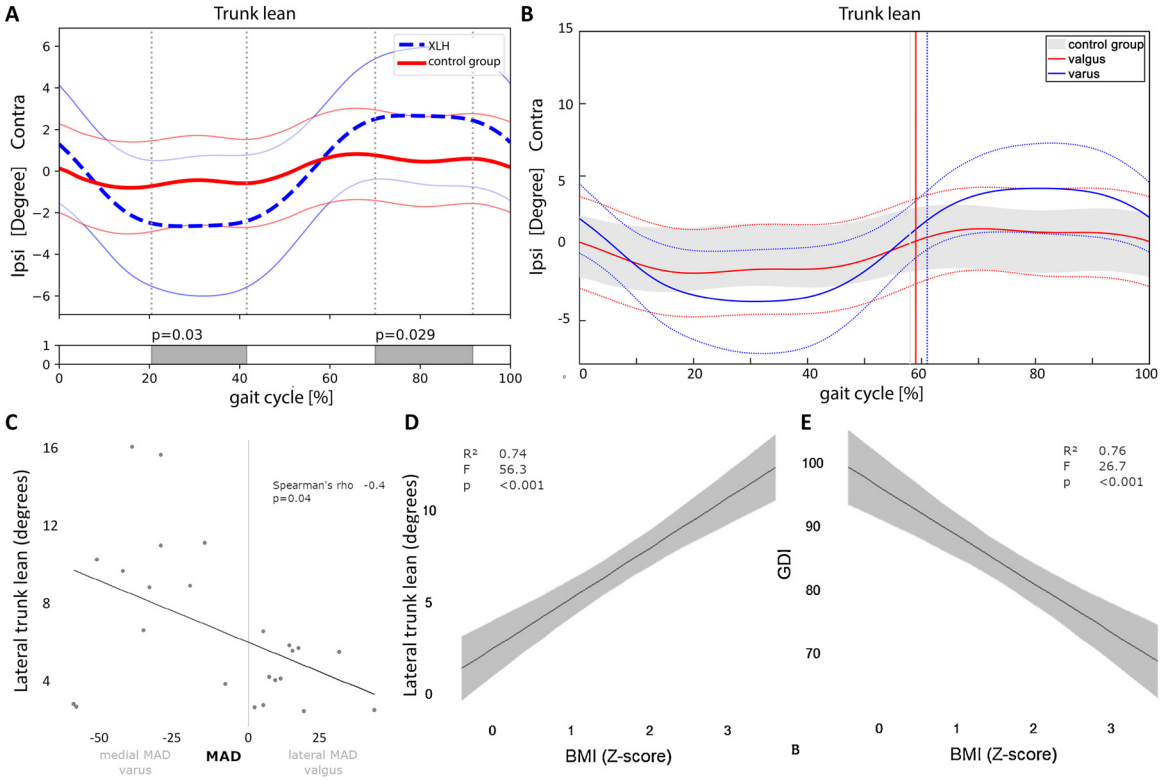

Fig. 2. A: XLH patients show increased lateral trunk lean during stance and swing phase. Dotted (blue) line indicates the XLH group (+ 1 SD), solid (red) line indicates the control group (+ 1 SD). Positive values equal a lateral thorax movement to the contralateral side, negative values equal a lateral thorax movement to the ipsilateral side. Gray bar indicates significant difference between **XLH group and control group** ($p < 0.05$), white bar indicates non-significance ($p > 0.05$). **B**: Patients with medial MAD (**MAD < -15° = varus knee deformity, n = 11 limbs**) show increased lateral trunk lean, whereas patients with lateral MAD **(MAD > 10 mm = valgus knee deformity, n = 7 limbs)** show movement within the normal range. Blue line indicates the XLH patients with medial MAD (varus deviation) (+ 1 SD), red line indicates the XLH patients with lateral MAD (+ 1 SD), grey band indicates the control group. Positive values equal a lateral thorax movement to the contralateral side, negative values equal a lateral thorax movement to the ipsilateral side. **C**: Correlation of MAD with lateral trunk lean shows an association of medial MAD (knee varus) with increased lateral trunk lean ROM. **D:** Linear regression model predicting lateral trunk lean by age-adjusted BMI Z-scores. 95 % confidence interval marked as grey area. Increase of BMI Z-score is associated with increased lateral trunk lean during gait. **E:** Linear regression model predicting and GDI by age-adjusted BMI Z-scores. 95 % confidence interval marked as grey area. Increase of BMI Z-score is associated with lower GDI (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

Table 3
Radiographic measurements (n = 12 children, 24 limbs), Blue = Varus, Red = Valgus, Yellow = Increased lateral trunk lean, radiographic reference [14].

	Femur				Tibia	
	MAD (mm)	mLPFA 85-95°	NSA 124-136°	mLDFA 85-90°	mMPTA 85-90°	mLDTA 86-92°
XLH1 left	17	85	134	87	92	92
XLH1 right	14	86	133	87	94	91
XLH2 left	-8	93	130	87	85	91
XLH2 right	9	91	135	86	87	90
XLH3 left	-20	92	147	88	77	93
XLH3 right	-34	96	143	88	71	91
XLH4 left	-15	95	128	100	88	88
XLH4 right	-30	91	136	106	90	87
XLH5 left	19	95	129	85	97	84
XLH5 right	43	91	120	79	103	86
XLH6 left	7	84	140	89	92	93
XLH6 right	11	85	136	88	94	96
XLH7 left	5	101	116	88	90	89
XLH7 right	2	107	110	89	90	88
XLH8 left	5	111	94	92	95	92
XLH8 right	-36	98	138	112	85	94
XLH9 left	-40	105	117	103	84	103
XLH9 right	-30	105	123	101	87	99
XLH10 left	15	88	123	82	89	88
XLH10 right	31	87	124	82	90	89
XLH11 left	-43	96	125	107	84	89
XLH11 right	-52	94	125	114	82	95
XLH12 left	-60	96	133	104	77	104
XLH12 right	-59	95	133	102	77	104
Mean	**-10,3**	**94,2**	**127,8**	**93,3**	**87,3**	**92,1**
Min	-60	84	94	79	71	84
Max	43	111	147	114	103	104
SD	29	7	11	10	7	6

needed.

A recent phase 3 study on novel FGF23 antibody treatment assessed the important symptom of bone deformities by improved lower limb deformity score using the Radiographic Global Impression of Change 7-point ordinal scale on knee radiographs. The study showed overall promising data regarding superiority to conventional conservative treatment options [4]. However, the applied Lower Limb deformity score using the Radiographic Global Impression of Change does not allow conclusions on disease specific deviations of lower limb deformity and the important issue of gait abnormalities in children with XLH. Treatment effects on complex lower limb deformities responsible for morbidity and healthcare costs in children with XLH remain marginally elucidated and need to be addressed more targeted in interventional studies. Based on our data, long leg standing radiographs and gait analysis allows a precise and minimal invasive quantification of axis deviations and gait alterations. The development of a new XLH specific scoring system based on gait parameters and radiographic parameters obtained in standardized long leg imaging may be beneficial in future interventional studies for this vulnerable cohort.

XLH-specific factors influencing gait quality have only sparsely been identified so far. Thacher et al. evaluated the walking ability in children with XLH using the 6-minute walk test (6MWT) and observed longer walking distances in children with lower RSS. Further, lower PODCI (Pediatric Outcomes Data Collection Instrument) sub scores in patients with higher RSS were reported as measure of physical functioning [26]. In this pediatric XLH cohort, correlation of RSS with GDI did not reach

statistical significance which is potentially a result of the limited patient number in this well-defined cohort. Nevertheless, we identified a strong association of age specific BMI Z-scores and GDI which was strengthened by ALP levels as covariate. This finding indicates the importance of metabolic control as well as compliance to treatment for maintenance of regular gait, as obese patients with biochemical signs of rachitic activity seem to be at high risk for severe gait abnormalities.

Considering the impact of lateral trunk lean on global gait impairment, a correction of varus knee deformity using guided growth (hemiepiphysiodesis of the distal lateral femur and/or proximal lateral tibia) could represent a minimally invasive option to ameliorate the waddling gait pattern in patients with XLH. Further, a strong correlation of lateral trunk lean with BMI might indicate obesity as a risk factor for the development of this specific gait impairment. Given that one third of pediatric patients with XLH have been reported to be overweight, metabolic control could be of high importance for maintaining regular gait patterns [27].

Given the association of metabolic control and gait quality, this study underlines the necessity of a multidisciplinary approach in the treatment and follow up of children with XLH. Due to the complex nature of bony deformities in XLH, management by pediatric orthopedic surgeons with subspecialization on deformity analysis and deformity correction is advisable. Gait analysis derived data contributes to our understanding of gait abnormalities and functional deficits in the complex deviations and should be implemented in the scientific setting. Based on our data, the effect of novel therapeutic approaches on the progression of deformities and gait impairment should be quantified by gait scores and standardized long leg radiographs.

6. Limitations

This study had a number of limitations. To precisely analyze deformities of lower limb especially in patients with XLH lateral view radiographs of both legs are necessary. Furthermore, torsional MRI or CT scans were not routinely obtained in all children. While a strong correlation of tibial torsion (CT) and knee rotation (gait analysis) has been described, femoral torsion (CT) and hip rotation (gait analysis) are only very weakly correlated [28]. Furthermore, gait analysis enables the detection of dynamic rotational components of the lower limb. Limited patient numbers were a result of strict inclusion criteria regarding previous extremity surgeries were applied to avoid iatrogenic bias on gait deviations. The resulting study size reflects a single specialist center cohort and exceeds the patient number of a recent study on gait in adult XLH patients with less rigid inclusion criteria [11]. In order to depict the spectrum of pediatric patients with XLH, we included children of all age groups during linear growth able to perform gait analysis (4–15 years of age). While the physiological development of tibial and femoral torsion is age related, especially in young children, the sample size does not allow age related subgroup analyses. However, disease specific gait deviations were seen in all age groups of this patient cohort indicating the presence of an XLH-specific impact on gait during the entire period of linear growth

7. Conclusion

This study for the first time analyzed naturally occurring gait deviations and bony deformity in children and adolescents with XLH. Complex deformities of the lower limbs including maltorsion and valgus - varus deformities were found in most patients of this surgery-naive XLH cohort. The detailed characterization of gait in this cohort can be used as basis for pediatric XLH gait reference data to allow comparison to therapeutic interventions. The association of commonly occurring gait deviations such as increased lateral trunk lean with knee deformities points to a role of minimal invasive guided growth surgery to correct frontal axis deviations improve gait abnormalities. Based on our data, we suggest the implementation of deformity parameters such as radiographic angles and mechanical axis deviation as well as instrumented gait analysis parameters in clinical studies on XLH to adequately evaluate conservative and surgical treatment effectiveness on this highly relevant clinical symptom. The characterization of abnormal gait in patients with XLH and identification of associated factors may aid to specifically address gait impairments in intervention studies and to target and improve mobility restrictions at earliest possible time points in multidisciplinary care.

Author statement

All authors made substantial contributions to the conception and design of the study, or acquisition of data, or analysis and interpretation of data and contributions to drafting the article.

Each of the authors has read and concurs with the content in the final manuscript. The material within has not been and will not be submitted for publication elsewhere except as an abstract.

Data availability

Data are available on request to the corresponding author.

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CRediT authorship contribution statement

Gabriel T. Mindler: Conceptualization, Methodology, Software, Investigation, Resources, Data curation, Writing - original draft, Visualization, Project administration, Writing - review & editing. **Andreas Kranzl:** Conceptualization, Methodology, Software, Validation, Resources, Formal analysis, Investigation, Data curation, Writing - review & editing, Visualization, Supervision. **Alexandra Stauffer:** Conceptualization, Software, Formal analysis, Investigation, Data curation, Writing - review & editing. **Gabriele Haeusler:** Conceptualization, Resources, Writing - review & editing, Supervision. **Rudolf Ganger:** Conceptualization, Resources, Writing - review & editing, Supervision. **Adalbert Raimann:** Conceptualization, Methodology, Software, Formal analysis, Resources, Investigation, Data curation, Writing - original draft, Visualization, Project administration, Writing - review & editing.

Declaration of Competing Interest

A. Raimann received honoraria from Kyowa Kirin for consultancies in 2018 not related to this study. The authors declare no further financial and personal relationships with other people or organisations that could inappropriately influence this work.

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Appendix A. Supplementary data

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