Impaired quality of life in adults with X-linked hypophosphatemia and skeletal symptoms

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Abstract

Objective: Adults with X-linked hypophosphatemia (XLH) may suffer from skeletal symptoms leading to functional disability. No data on their quality of life (QoL) have been reported so far. Our objectives were to evaluate the QoL and its determinants in XLH adults.

Patients and methods: We conducted a prospective study in XLH adults, who consulted for musculoskeletal symptoms between 2013 and 2014. We assessed their QoL using HAQ, RAPID3 and SF36, and analysed the variables associated with low QoL. We compared their QoL to that of patients affected with axial spondyloarthritis (ax-SpA) (paired on age and gender), a rheumatologic disorder with a known low QoL.

Results: Fifty-two XLH adults (37 women (71.1%); mean age 41.8 ± 13.3 years) were included; 44 (84.6%) patients had an altered QoL. Increased age and presence of structural lesions were significantly associated with worse QoL (HAQ, RAPID3) ($P < 0.05$). Presence of enthesopathies was significantly associated with worse RAPID3 (OR = 4.45 (1.09–18.29), $P = 0.038$). Treatment with phosphate supplements and vitamin D in XLH adults were significantly associated with a better SF36-mental component score (OR = 0.14 (0.03–0.57), $P = 0.007$ and OR = 0.26 (0.07–0.98), $P = 0.047$ respectively). QoL was significantly worse in XLH than in ax-SpA adults (VAS pain, SF36-PCS, RAPID3) ($P < 0.05$).

Conclusion: Our study showed i) QoL of XLH adults is altered and significantly worse than that of ax-SpA patients (VAS pain, SF36-PCS and RAPID3), ii) structural lesions and especially enthesopathies are associated with a worse QoL and iii) treatment using phosphate supplements and/or vitamin D is associated with a better mental health score.

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Introduction

X-linked hypophosphatemia (XLH), the most common heritable form of rickets or osteomalacia, is due to loss-of-function mutations in the phosphate-regulating gene with homologies to endopeptidase on the X chromosome (PHEX), which results in elevated blood levels of fibroblast growth factor 23 (FGF23), phosphate wasting, hypophosphatemia and decreased vitamin D hydroxylation in the kidney. XLH has an incidence of 3.9/100 000 live births and a prevalence of 4.8/100 000 (1).

In children, phenotypic expression includes variable degrees of growth retardation, bone pain and deformities, impaired dental mineralisation, delayed walking, cranios-tenosis, waddling gait, leg bowing and rickets. Therapy with phosphate salts and vitamin D analogs aim at reducing bone pain, improving dentition, correcting leg deformities, improving adult height and decreasing the number of surgeries (2, 3). Initiation at early ages is recommended as the early initiation of treatment optimises final body height results (2, 3).

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Adult patients with XLH (XLH adults) can be affected not only by skeletal complications related to spontaneous fractures because of persistent osteomalacia but also early osteoarthritis and enthesopathies, for which the severity of symptoms and of structural involvement is variable (3, 4, 5, 6). The disease outcome in adults remains inadequately described. Most adults are treated with phosphate supplements and vitamin D analogs to reduce extent of osteomalacia and to improve fractures healing or surgery recovery; however, there is no consensus on the indications and duration of treatment in adults. Serum alkaline phosphatase activity is measured to quantify the extent of osteomalacia; some biological tests (25 OH vitamin D, calcaemia, phosphatemia, calciuria, phosphaturia, parathyroid hormone serum level) are performed for the monitoring of XLH, in order to avoid some complications such as hypercalciuria or hyperparathyroidism (2, 3).

On the other hand, other long-term skeletal complications (osteoarthritis and enthesopathies) are also responsible for musculoskeletal pain and fatigue likely leading to disability and altered quality of life (QoL) (2). Visual analogic pain scales may help to quantify the degree of pain and disability but are not appropriate to assess the disease burden.

The objectives of our study were to evaluate the QoL of XLH adults with skeletal symptoms and to identify which variables were associated with an altered QoL. To evaluate the severity of the functional disability and its impact on the QoL, we compared the QoL of XLH adults to that of adults affected with axial spondyloarthritis (ax-SpA). Ax-SpA is a chronic rheumatic disease affecting young patients with similar radiological phenotype of enthesopathies and for which the low scores of QoL due to function disability are already known. Our ultimate goal is to provide QoL and its determinants as novel outcomes for the monitoring of therapeutic interventions in XLH.

Patients and methods

Study design

Descriptive prospective study in a tertiary centre.

Participants

This study was conducted in XLH adults carrying a PHEX mutation; all of them were referred for musculoskeletal symptoms in our Rheumatology department, between December 2013 and December 2014. All participants

received written information and gave oral consent for use of their data, which were obtained as part of routine assessment in such patients. No extra blood samples or X-rays exams were performed for this study.

Clinical, biological and radiological parameters

The following variables were assessed using interviews and physical exams for each patient by the rheumatologist: age at visit, age at diagnosis, family history of XLH, history of orthopaedic surgery of lower limbs, vitamin D analogs and phosphate supplements during childhood, pain related to musculoskeletal location at time of assessment, pain intensity using Visual Analogic Scale (VAS), fatigue, lower limbs deformations, reported dental defects, current treatment with vitamin D, vitamin D analogs and/or phosphate supplements, biological data (calcaemia, phosphatemia, serum alkaline phosphatase, parathyroid hormone (PTH), 25OH vitamin D).

Imaging of the whole skeleton was performed using the EOS biplane X-ray imaging, in an upright weight-bearing position providing a high quality image with less radiation than standard imaging techniques. The quality of the image is similar to computed radiography and digital radiography (7). EOS can image the full length of the body, removing the need for digital stitching (7). Presence of osteoarthritis of spine, hip and knee (defined as formation of osteophytes on joint margins or narrowing of joint cartilage associated with sclerosis of subchondral bone or small pseudocystic areas with sclerotic walls in subchondral bone or altered shape of the bone ends) (8), enthesopathies (defined as bone proliferation at site of ligament attachments or calcification of ligaments) (9, 10) and sequelae of insufficiency fractures (defined by incomplete cortical break sometimes associated with a periosteal reaction without history of trauma (11) were evaluated, on the whole skeleton except the skull (Fig. 1), by two experienced rheumatologists blinded to each other who adjudicated any discrepancy. A training session was done before the start of the study (12, 13, 14, 15).

Forty-three patients (82.7%) had full body EOS imaging, the others had X-rays of the region of interest. Nine patients (17.3%) had X-rays recently performed at the time of referral, and EOS imaging was not performed for them.

Health Related QoL measurements

Pain was quantified at the time of evaluation on a VAS from 0 (no pain) to 100 (worst pain).

Figure 1

X-ray features in XLH adults. (a) Osteoarthritis. (b) Enthesopathies: 1/lumbar spine, 2/pelvis. (c) Fractures.

Health Related QoL (HRQoL) was assessed using three validated questionnaires, completed by the patient at the time of visit: health assessment questionnaire (HAQ), Routine Assessment of Patient Index 3 (RAPID3) and short form 36 (SF36). None of them have been tested in XLH adults. We excluded patients unable to read and understand the questionnaires.

HAQ ► The HAQ concerns functional disability and pain in rheumatic diseases (16). Physical function is assessed with 20 questions about daily activities grouped in eight categories: dressing and grooming, arising, eating, walking, hygiene, reach and grip. The final score, ranging from 0 (no difficulty in performing the task) to 3 (failure to achieve the task), corresponds to the mean of the sum of these eight category scores (each category score obtained by using the highest sub-category score) and takes into account the use of aids or devices (16). HAQ has been used in rheumatic diseases (rheumatoid arthritis, spondyloarthritis) and compared with healthy controls (17). HAQ is considered low when score is higher than 0.5 (18).

RAPID3 ► RAPID3 is a composite index assessing three domains: physical function, pain and disease activity. Each domain is scored from 0 to 10 and the final score is the sum of the three domains. High scores represent the worse altered health state (19, 20, 21). RAPID 3 was first used in rheumatoid arthritis (RA); comparison of RAPID 3 with RA activity score (DAS28) shows that they determine

outcomes in similar categories, such as remission and low, moderate and high disease activity. A score > 12 indicates high severity, 6–12 indicates moderate severity and 3–6 indicates low severity. A score of < 3 indicates remission. We chose the threshold > 6 (moderate severity) for low QoL in our population as done in other studies (20, 21).

SF36 ► The SF36 is a generic questionnaire of QoL with 36 questions divided into eight domains, scored from 0 (worst QoL) to 100 (best QoL): physical function (PF), bodily pain (BP), vitality (VT), social function (SF), mental health (MH), general health (GH), role physical (RP), role emotional (RE). The SF36 can be presented as the physical component score (PCS=PF+RP+BP+GH) and mental component score (MCS=MH+RE+SF+VT). The final score is the mean of the sum scores for the domains (22).

There is no threshold value delimiting low and normal QoL (22).

Axial spondyloarthritis control group

The control group was constituted of ax-SpA adults followed in the same department during the same period and matched for age and gender (23, 24). These patients gave their oral consent for the participation in this study. The HAQ, RAPID3 and SF36 scores have been validated in ax-SpA (25, 26).

Statistical analysis

First, we described the characteristics of the XLH adult patients and results of QoL (mean values ($\pm$ S.D.)). In our study, altered QoL was defined for each index: HAQ > 0.5 (17, 18), RAPID3 > 6 (19, 20, 21), SF 36 values < median values (in absence of consensual threshold value, in the literature). We also defined a composite criterion of altered QoL as having an HAQ > 0.5, or an RAPID3 > 6, or one of the SF36 component scores < median value. A logistic regression was used to assess the variables significantly associated with altered QoL. The variables tested were: age, gender, family history of XLH, history of orthopaedic lower limb surgery, history of treatment in childhood (combination of phosphate supplements and vitamin D analogs), duration of disease (time since diagnosis), clinical symptoms (musculoskeletal pain, fractures, musculoskeletal fatigue, reported dental defects, deformation of lower limbs), radiological lesions (osteoarthritis, enthesopathies, sequelae of insufficiency fractures), current treatment with phosphate supplements, vitamin D,

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vitamin D analogs, analgesics, non-steroidal anti-inflammatory drugs and/or physiotherapy.

We compared the QoL of XLH adults to that of the ax-SpA adults using a Student test.

P value <0.05 was considered as statistically significant. The statistical analysis was performed using the SAS Software SAS (version 9.3; SAS Institute, Cary, NC, USA).

Results

Characteristics of the XLH adult patients

In total, 52 XLH adults (71.1% female, mean age of 41.8 ± 13.3 years), with a mean (±s.d.) disease duration of 34.6 ± 16.5 years, were referred to our department for skeletal symptoms, and all of them were included in the study. Their characteristics are described in Table 1. At the time of evaluation, musculoskeletal pain and fatigue were reported in 90.4 and 86.0% of patients respectively. Radiological abnormalities were present in 32 patients (61.5%): osteoarthritis in 85.4%, enthesopathies in 64.0%

and sequelae of femoral insufficiency fractures in 36.0%. At the time of QoL evaluation, 64.6, 59.2 and 66.7% patients were receiving phosphate supplements, vitamin D or vitamin D analogs respectively. Only 31.2 and 23.9% were receiving analgesics and non-steroidal anti-inflammatory drugs (NSAIDs) respectively.

QoL results in XLH patients

Mean (±s.d.) values of VAS pain, HAQ, RAPID 3, SF36 PCS and SF36 MCS are reported in Table 2.

Twenty-nine (55.8%), 40 (76.9%), 26 (50%) and 26 (50%) XLH adults had a low QoL defined by either an HAQ (>0.5), an RAPID3 (>6), an SF36-PCS (<42.71, median value) or an SF36-MCS (<57.71, median value) respectively. Forty-four (84.6%) XLH adults had a low QoL defined by the composite score: HAQ (>0.5) or RAPID3 (>6) or SF36-PCS (<42.71) or SF36-MCS (<57.71).

Variables associated with a low QoL ► For each questionnaire of QoL, age was significantly associated with

Table 1 Characteristics of XLH adults included in the study.

Variables	XLH adults
Patients (n)	52
Age (years), mean (±s.d.)	41.8 (±13.3)
Gender (n) (% female)	37 (71.1)
Family history of XLH (n) (%)	26 (72.2)
History of orthopaedic lower limbs surgery (n) (%)	33 (63.5)
Treatment during childhood (n) (%)	31 (73.8)
Time since diagnosis (years), mean y (±s.d.)	34.6 (±16.5)
History of fractures (n) (%)	16 (40.0)
Deformations of lower limbs (n) (%)	44 (95.6)
Self reported dental defects (n) (%)	20 (62.5)
Phosphorous (mmol/l), mean (±s.d.) (normal range 0.8–1.5)	0.56 (±0.08)
Calcium (mmol/l), mean (±s.d.) (normal range 2.2–2.6)	2.31 (±0.09)
PTH (pg/ml), mean (±s.d.) (normal range 10–60)	62.8 (±28.7)
25OH vitamin D (ng/ml) mean (±s.d.) (normal range 10–45)	32.5 (±15.2)
Alkaline phosphatase (IU/l), mean (±s.d.) (normal range 40–100)	80.0 (±26.9)
Structural lesions, n/n of patients with data available (%)	32/52 (61.5)
Radiological osteoarthritis	41/48 (85.4)
n/n of patients with data available (%)	
Spine	29/46 (63.0)
Hip	37/47 (78.7)
Knee	22/47 (46.8)
Enthesopathies, n/n of patients with data available (%)	32/50 (64.0)
Radiological fractures, n/n of patients with data available (%)	18/50 (36.0)
Current treatment (n) (%)	
Phosphate supplements	31 (64.6)
Vitamin D	29 (59.2)
Vitamin D analogs	32 (66.7)
Analgesics	15 (31.2)
NSAIDs	11 (23.9)
Physiotherapy	27 (57.4)

XLH, X-linked hypophosphatemia; n, number; NSAIDs, non steroidal anti-inflammatory drugs.

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Table 2 Comparison of quality of life of XLH and ax-SpA populations. Means ($\pm$ s.d.) are reported in the table.

Variables	XLH	Ax-SpA	P value
HAQ (0–3)	0.69 (0.56)	0.66 (0.62)	0.523
RAPID3 (0–30)	12.1 (6.4)	8.9 (6.0)	0.017
SF36 PCS (0–100)	49.5 (20.5)	58.3 (21.2)	0.029
SF36 PF	60.6 (23.7)	71.6 (21.7)	0.023
SF36 RP	40.4 (37.7)	45.7 (37.9)	0.534
SF36 BP	54.3 (23.6)	66.8 (23.8)	0.010
SF36 GH	42.9 (18.4)	49.0 (19.7)	0.060
SF36 MCS (0–100)	57.9 (21.3)	63.1 (23.0)	0.207
SF36 VT	42.5 (19.9)	47.8 (20.7)	0.204
SF36 SF	70.4 (20.3)	76.9 (23.7)	0.077
SF36 RE	59.0 (45.1)	62.2 (46.7)	0.670
SF36 MH	59.7 (17.7)	65.6 (20.6)	0.217
VAS pain (0–100)	50.0 (26.0)	36.0 (26.0)	0.008

XLH, X-linked hypophosphatemia; Ax-SpA, axial spondyloarthritis; HAQ, health assessment questionnaire; RAPID3, routine assessment of patient index data 3; SF36, short form 36; PCS, physical component score; MCS, mental component score; BP, bodily pain; PF, physical function; RP, role physical; GH, general health; VT, vitality; SF, social functioning; RE, role emotional; MH, mental health; VAS, visual analogic scale.

HAQ > 0.5 and RAPID3 > 6. Women described worse QoL than males in terms of RAPID3 and SF36-PCS. Dental defects were significantly associated with worse QoL reported by HAQ and RAPID3. Structural lesions (all lesions as a whole) were significantly associated with worse scores of HAQ and RAPID3. Enthesopathies were significantly associated with worse scores of RAPID3. Treatment with phosphate supplements and vitamin D in XLH adults were significantly associated with better SF36-MCS scores (Table 3).

Age, female gender, musculoskeletal fatigue and enthesopathies were significantly associated with a

reduced QoL defined by the composite score (HAQ > 0.5 or RAPID3 > 6 or SF36 < median value) (Table 3).

Comparison of QoL in XLH and ax-SpA populations

Ax-SpA population ► A total of 52 patients (63.6% female, mean age of 45.3 ± 12.7 years) with ax-SpA matched for age and gender, were included in the study as a control group. The mean duration of their disease was 13.3 ± 9.5 years. The disease activity of the ax-SpA patients was reasonably well controlled as judged by the mean ($\pm$ s.d.) values of the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Bath Ankylosing Spondylitis Functional Index (BASFI) scores of 32.3 ± 20.0 and 28.4 ± 23.8 respectively, and by the C-reactive protein mean ($\pm$ s.d.) value of $4.61 (\pm 7.10)$ mg/l. Thirty-eight (73.1%) patients were receiving TNF α -blockers; 15 (28.8%) and 22 (42.3%) patients were treated with analgesics and NSAIDs respectively. Forty-eight (92.3%) patients had structural lesions: 28.0, 75.0 and 77.1% presented with syndesmo-phytes, radiological sacro-iliitis and MRI sacroiliitis respectively. The prevalence of the spinal enthesopathies was lower in the ax-SpA adults than that of XLH adults (28% vs 64% respectively, $P=0.0001$).

QoL of XLH and comparison with ax-SpA ► Average HAQ scores were similar in the two groups of patients (Table 2). However, VAS pain was higher in XLH than in ax-SpA adults (50.0 vs 36.0 , $P=0.008$). Although there was no difference in the percentage of patients receiving analgesics and NSAIDs between the two groups, QoL was

Table 3 Variables associated with worse QoL in XLH adults using logistic regression.

Assessment of an altered quality of life	Variables significantly associated	Odds ratio	P value
HAQ > 0.5	Age	1.06 (1.00–1.12)	0.036
	Dental defects	7.00 (1.19–41.36)	0.032
	Structural lesions	6.75 (1.19–38.40)	0.031
RAPID3 > 6	Age	1.07 (1.00–1.14)	0.048
	Female gender	5.60 (1.40–22.36)	0.015
	Dental defects	13.57 (1.34–137.45)	0.027
	Structural lesions	6.43 (1.37–30.11)	0.018
	Enthesopathies	4.45 (1.09–18.29)	0.038
SF36-PCS < 42.71	Female gender	4.03 (1.08–15.09)	0.038
SF36-MCS < 57.71	Vitamin D treatment	0.26 (0.07–0.98)	0.047
	Phosphate supplements treatment	0.14 (0.03–0.57)	0.007
Composite criterion ^a	Age	1.11 (1.01–1.22)	0.031
	Female gender	5.67 (1.15–27.94)	0.033
	Musculoskeletal fatigue	8.25 (1.23–55.57)	0.030
	Enthesopathies	7.50 (1.32–42.50)	0.023

QoL, quality of life; XLH, X-linked hypophosphatemia; HAQ, health assessment questionnaire; RAPID3, routine assessment of patient index data 3; SF36, short form 36; PCS, physical component score; MCS, mental component score.

^aComposite criterion defined as HAQ > 0.5 or RAPID3 > 6 or SF36-PCS < median value or SF36-MCS < median value.

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significantly worse in XLH than in ax-SpA patients, with a higher RAPID3 (12.1 vs 8.9, $P=0.017$) and a lower SF36 PCS (49.5 vs 58.3, $P=0.029$).

Discussion

This is the first study of QoL impairment conducted in adult patients with XLH. Our study, performed in one centre on 52 consecutive patients over one year shows that young XLH adults with musculoskeletal symptoms display a severely impaired QoL, confirming that XLH can be a physically disabling condition. Age, female gender and presence of enthesopathies were significantly associated with impaired QoL.

Comparison with general population and other chronic rheumatic diseases

We compared QoL of XLH patients with available data on the general population and populations of patients with chronic musculoskeletal diseases. These indirect comparisons show that XLH adults have a lower QoL than the general population (26, 27) and their QoL is close to that

of patients with chronic diseases (Table 4). Indeed, the mean values of QoL of XLH adults are similar to those reported in patients with rheumatoid arthritis, another severe disabling condition, assessed by SF36 (28), HAQ (29) and RAPID3 (18, 30). Patients with osteoarthritis presented similar (medical stage of osteoarthritis) or worse (surgical stage of osteoarthritis) QoL than that of XLH adults, in terms of RAPID3 (30), HAQ (31) and SF36 (32). Patients with juvenile idiopathic arthritis have, on average, better QoL than XLH adults (29, 32).

We compared the XLH adults to ax-SpA patients because structural damages are comparable in both diseases including ossifications and enthesopathies (Table 2). As expected, VAS global pain was lower in ax-SpA as 73.1% of them were treated with TNF-blockers. Only a minority of XLH patients were taking analgesics or NSAIDs at the time of referral, as most of them considered them as ineffective if in their chronic pain. However, XLH adults had lower physical function and abilities. Interestingly, we did not observe any difference between XLH and ax-SpA patients on SF36-mental component score, suggesting that XLH adults were coping with their physical limitations. Although they had a poor chronic

Table 4 Health related quality of life scores for our X-linked hypophosphatemia (XLH) patients, French population and rheumatologic disease populations.

	Health related quality of life scores, mean (s.d.)					
	XLH	French population	Rheumatoid arthritis	Juvenile idiopathic arthritis	Osteoarthritis	
					MS	SS
HAQ (0–3)						
n		59 ^a	99 ^c	9 ^c	44 ^c	
Mean (s.d.)	0.69 (0.56)	0.152	0.843 (0.639)	0.232 (0.561)	0.561 (0.518)	
RAPID3 (0–30)		NA		NA		
n			174 ^d		113 ^d	
Mean (s.d.)	12.1 (6.4)		12.2 (8.0)		12.1 (6.2)	
SF36 (0–100)						
n		391 ^b	137 ^e	32 ^f	139 ^g	97 ^g
PF	60.6 (23.7)	83.7 (21)	35.0 (50.0)	77.5	48.8 (23.5)	35.8 (21.4)
RP	40.4 (37.7)	80.3 (31)	0.0 (50.0)	50	41.2 (40.1)	22.0 (31.9)
BP	54.3 (23.6)	69.6 (14)	33.3 (33.3)	40	42.3 (20.8)	34.0 (16.7)
GH	42.9 (18.4)	66.4 (19)	47.0 (37.0)	45	51.2 (19.8)	54.3 (16.5)
VT	42.5 (19.9)	57.6 (19)	45.0 (25.0)	65	43.8 (19.8)	37.1 (15.0)
SF	70.4 (20.3)	79.0 (31)	66.7 (44.5)	50	48.8 (23.5)	35.8 (21.4)
RE	59.0 (45.1)	81.6 (32)	66.7 (100.0)	40	49.6 (43.7)	26.9 (38.6)
MH	59.7 (17.7)	66.5 (16)	68.0 (28.0)	70	59.0 (21.1)	52.3 (19.0)

MS, medical stage; SS, surgical stage; BP, bodily pain; PF, physical function; RP, role physical; GH, general health; VT, vitality; SF, social functioning; RE, role emotional; MH, mental health; NA, not available.

^a(17)

^b(29)

^c(30)

^d(27)

^e(28)

^f(32)

^g(31)

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physical condition, XLH adults seemed to maintain appropriate emotional and behavioural mental health.

We have also found, in our study, that the treatment with phosphate supplements and/or vitamin D during adulthood was associated with a better mental health in XLH adults. However, it is not possible to determine if the therapy allowed patients to feel better or if patients with better mental health are more susceptible to take these treatments. The link between phosphate homeostasis and functional symptoms such as fatigue has been suggested but there is no evidence of causality (33).

Prevalence of structural lesions and mechanisms of formation

In our cohort of young XLH adults, 85.4% of the patients displayed early features of osteoarthritis of the lumbar spine, the hip or the knees. Enthesopathies were significantly more frequent in XLH than in ax-SpA patients (64% vs 28%). In a Danish study conducted on 35 adult patients (68.6% females), enthesopathies and calcifications of the collateral ligaments of the spine were observed in 84% of the patients aged 40 years or more (6).

It has been shown that the early initiation of treatment with a combination of phosphate supplements and vitamin D analogs during childhood progressively corrects the leg deformities (34). However, the effect of treatment in adults on skeletal complications (osteoarthritis, enthesopathies) is still unknown (2, 35).

Different mechanisms can explain the new bone formation in XLH. In ax-SpA, there is some evidence that inflammation precedes radiographic progression in the skeleton (36, 37) or that new bone formation can be considered as a repair mechanism associated with the transformation of new inflammatory lesions to fatty degenerative changes (38, 39). However, formation of enthesophytes can occur in absence of inflammation and may be due to excess of mechanical stress and composition of the bone matrix. This feature has already been described in a mouse model of XLH, where a histological analysis of affected enthesis was performed. The mineralisation of enthesis was not due to osteoblastic formation but to an increased expression of FGFR3 and Klotho in the fibrocartilage leading to new bone formation and hence enthesophytes (35).

Limitations and strengths

As a tertiary referral centre, we deal with patients with more severe disease and our group of patients may have

more disability than the average adult population affected with XLH. Our data cannot be generalised to all XLH patients. We compared XLH adults to ax-SpA patients because of the similarities of skeletal lesions, but we recognise that this does not explore the difference of QoL with age and sex-matched healthy controls.

QoL completion by a patient is inevitably impacted by external factors (disability due to comorbidities, psychological impact of a chronic disease) and may also be fluctuating with evaluation time. As our study was initially designed to assess QoL of XLH patients whatever the context of the patients, we did not adjust on comorbidities and psychological diagnoses as confounding factors. Data on QoL outcomes were obtained 15–20 years ago without any recent normative values and thus may not be still valid.

We recruited a large sample of patients who were referred through the network of the National Reference Centre for Rare Disorders of the Mineral Metabolism as soon as a disabling condition was detected. Another major strength of our study is the systematic use of questionnaires validated in chronic musculoskeletal diseases. We chose the questionnaires that are the most frequently used in rheumatic diseases. SF36 and RAPID3 are general questionnaires whereas HAQ is a specific one, assessing physical function. We recognise that none of these questionnaires have been validated in XLH. However, we circumvented this issue by comparing the XLH adult group to the ax-SpA adult group, for which these questionnaires have been previously validated. In our study, the difference between patients and ax-SpA was the largest with RAPID3. The RAPID3 score, computable in 5 s, has been well correlated with disease activity in rheumatoid arthritis and might be able to distinguish adequate and non-adequate response to treatment with disease modifying anti-rheumatic drugs (40, 41). Its sensitivity to change in other diseases, such as XLH, needs further prospective studies.

Novel therapies are under development in XLH such as anti-FGF23 which showed promising results, in mice, in improving mineralisation and cartilage development, promoting growth, improving muscle strength and motor activity (42) and, in humans, in improving serum phosphate (43). Although it is obvious that XLH children would benefit from this new treatment, the questions remains unanswered if there is an indication of treating XLH adults and if so which outcomes are relevant in adults. Our study shows that enthesopathies are a major determinant of the QoL and of the physical function in XLH adults. Therefore, it is relevant to assess the worst domains of QoL in order to manage appropriately;

moreover, QoL could be a surrogate outcome to evaluate efficacy of new treatments.

Our study conducted in symptomatic adults with XLH shows that QoL is severely impaired, even more than that of young adults affected with axial spondyloarthritis. Structural lesions (osteoarthritis, enthesopathies and insufficiency bone fractures) are frequent in young XLH adults and are associated with the altered QoL, especially for enthesopathies. Phosphate supplements and/or vitamin D are associated with a better mental health score. QoL assessment is clinically relevant for the assessment of treatment outcomes in this adult population.

Declaration of interest

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

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Author contribution statement

H Che participated in study conception and design, acquisition of data, analysis and interpretation of data; was also involved in drafting the manuscript; gave final approval of the version to be published and agreed to be accountable for all aspects of the work. C Roux participated in study conception and design, analysis and interpretation of data; was involved in revising the manuscript critically; gave final approval of the version to be published and agreed to be accountable for all aspects of the work. A Etcheto participated in acquisition of data, analysis and interpretation of data; was involved in drafting the manuscript; gave final approval of the version to be published and agreed to be accountable for all aspects of the work. A Rothenbuhler participated in acquisition of data, analysis and interpretation of data; was involved in revising the manuscript critically; gave final approval of the version to be published and agreed to be accountable for all aspects of the work. P Kamenicky participated in acquisition of data, analysis and interpretation of data; was involved in revising the manuscript critically; gave final approval of the version to be published and agreed to be accountable for all aspects of the work. A Linglart participated in acquisition of data, analysis and interpretation of data; was involved in revising the manuscript critically; gave final approval of the version to be published and agreed to be accountable for all aspects of the work. K Briot participated in study conception and design, acquisition of data, analysis and interpretation of data; was involved in drafting the manuscript and in revising the manuscript critically; gave final approval of the version to be published and agreed to be accountable for all aspects of the work.

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