

# Health-related quality of life in children and adults with X-linked hypophosphatemia

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## Abstract

Background X-linked hypophosphatemia (XLH) is an inherited type of severe rickets leading to deformities and can sometimes become a debilitating condition. Its impact on health-related quality of life (HRQoL) has not been extensively studied.

Results Using standardized questionnaires in 21 children and 29 adults with confirmed XLH, we observed significant impaired HRQoL. Children had moderate problems in walking about (61.9%), washing or dressing themselves (9.52%), and performing their usual activities (33.33%). They also felt moderate pain or discomfort (61.9%) and were moderately anxious or depressed (23.81%). The mean EQ-5D-3L/EQ-5D-3L proxy index was  $0.79 \pm 0.15$  and the mean VAS score was  $68.33 \pm 16.61$ . Adults had lower HRQoL, particularly with problems in walking (93%, with 3.45% unable to walk independently) and pain (86%, with 3.45% experiencing extreme pain). They also reported problems when carrying out their usual activities (80%) and washing or dressing themselves (>50%), and 65% of adult patients reported symptoms of anxiety and/or depression. The differences compared with the general Spanish population were significant, especially in the mobility and pain/discomfort dimensions of the EQ-5D-5L instrument. Caregivers and parents showed mild reduction in HRQoL, with a mean EQ-5D-5L index value ( $0.82 \pm 0.16$ ) and a mean VAS score ( $75.48 \pm 17.24$ ) smaller than that found in the general Spanish population. Conclusions X-linked hypophosphatemia reduced health-related quality of life despite treatment. These results evidenced limitations of conventional treatment in preventing disease complications, which in turn impaired quality of life in pediatric and adult patients.

## Background

Health-related quality of life (HRQoL) in patients with rare diseases and their caregivers has not been widely studied [1]. In a study of 1218 adults with different rare diseases, HRQoL was found to be lower than that of both the general US population and patients with common chronic diseases [2]. Low HRQoL in rare diseases is mainly caused by diagnostic delay and treatment difficulties. It is of note that rare diseases affect not only patients and caregivers but also health professionals in Spain and throughout the world [3-5].

X-linked hypophosphatemia (XLH) is a severe, debilitating and deforming inherited condition. It is a rare disease, with an incidence of 1:20,000 [6]. It is the most common form of hereditary hypophosphatemia and is caused by inactivating mutations in the phosphate regulating endopeptidase homolog (*PHEX*) gene [7]. This mutation produces increased levels of fibroblast growth factor 23 (FGF23), a phosphate-regulating hormone that decreases renal reabsorption of phosphate and alters bone mineralization. As a result the affected subjects develop hypophosphataemia, rickets or osteomalacia, skeletal deformities and diminution of growth. Clinical symptoms commonly develop during the first or second year of life, coinciding with walking onset. Clinical manifestations vary in severity [8] and many of them are considered to be related to increased levels of FGF23 [9]. Disease manifestations in children include motor delay, impaired growth, abnormal gait, skeletal deformities in lower limbs, craniosynostosis and dental complications. Adult patients also have skeletal pain and significant associated morbidity, frequently related to early osteoarthritis, enthesopathies, spinal stenosis or pseudofractures, among others. These complications clearly worsen the HRQoL of these subjects [8]. Early diagnosis and optimal treatment are paramount to control the disease, avoid complications, and maintain or improve HRQoL [10].

There are few studies on HRQoL in patients with XLH and their caregivers [11-13]. We therefore analyzed the HRQoL of patients with XLH in Spain in order to improve the care of patients with this rare disease.

## Results

The study was conducted from September 2017 to May 2018, with patient inclusion carried out from December 2017 to April 2018. Fifty patients participated in the study: 21 children (<18 years) accompanied by their respective parents or caregivers, and 29 adults. These latter were 21 women and 8 men, with a mean age of  $42.21 \pm 16.18$  years, and with 5 patients (all women) aged 60 years or older.

The results of EuroQoL-5 dimensions-3 levels (EQ-5D-3L) and EQ-5D-3L proxy (Figure 1 and Additional file 1) showed that more than 60% of children had walking difficulties and also reported pain or discomfort. Almost 34% of children had difficulties

performing their usual activities, nearly 24% felt anxious or depressed, and almost 10% had some difficulties with washing or dressing themselves. The mean EQ-5D-3L (and EQ-5D-3L proxy) index was  $0.788 \pm 0.153$  and the mean visual analog scale (VAS) score was  $68.33 \pm 16.06$ . No data regarding EQ-5D-3L and EQ-5D-3L proxy in children were available in the 2011 and 2017 National Health Surveys in Spain (ENSE).

Mobility was also the most affected dimension in adults with XLH, with 93% of patients reporting walking difficulties. Pain/discomfort was reported by 86% of patients, with severe or extreme pain in more than 40%. In addition, 80% of patients reported difficulties doing their usual activities, 65% felt some level of anxiety/depression and more than 50% of patients had difficulties in taking care of themselves (Figure 2 and Additional file 2). The mean EuroQoL-5 Dimensions-5 Levels (EQ-5D-5L) index was  $0.562 \pm 0.28$  and the mean VAS score was  $55.96 \pm 20.86$ .

On comparing our results with those of the 2011-2012 ENSE [14], adult patients with XLH had a poorer HRQoL than the general Spanish population (Table 1), with differences in all dimensions. In order of difficulty/severity these differences were mobility, pain/discomfort, usual activities, self-care and anxiety/depression. Walking difficulties were reported by 93.10% of patients with XLH compared with 14.28% of the general population, including 3.45% and 0.82%, respectively, who were unable to walk. Pain/discomfort was described by nearly 87% of patients compared with 25% of the general population. Differences between patients and the general population were especially marked for moderate and severe pain. Nearly 80% of patients with XLH presented some difficulties in performing their usual activities while only 11% of the general population reported difficulties. More than 50% of patients with XLH reported some hardship with self-care compared with only 6% of the general population. Finally, more than 65% of patients with XLH but only 15% of the general population had some level of depression/anxiety. The worse HRQoL in adult patients with XLH was also expressed by the very different mean EQ-5D-5L index:  $0.562 \pm 0.28$  in patients and  $0.914 \pm 0.15$  in the general population [14]. Similarly, the mean VAS score in adult patients with XLH ( $55.96 \pm 20.86$ ) was much lower than that of the general population ( $77.53 \pm 18.60$ ) [14].

For caregivers and parents (Additional file 3), the EQ-5D-5L index was  $0.821 \pm 0.157$  and the VAS score was  $75.47 \pm 17.24$ . These values were slightly lower than those found in the general Spanish population:  $0.914 \pm 0.15$  and  $77.53 \pm 18.60$ , respectively [14].

## Discussion

This study showed HRQoL impairment in Spanish pediatric and adult patients with XLH. Pediatric patients reported difficulties in the five dimensions of the EQ-5D-3L and EQ-5D-3L proxy. More than 60% of pediatric patients had moderate walking difficulties and also reported moderate pain/discomfort. Reduction of HRQoL was notably larger in adult patients, with significant impairment in all EQ-5D-5L dimensions. Impairment was especially marked in the mobility dimension, with nearly 25% of patients having severe or extreme problems, and in the pain/discomfort dimension, with 40% of patients having severe or extreme pain. There were also evident difficulties in performing usual activities, including self-care, as well as symptoms of anxiety and/or depression. Compared with the general population, HRQoL impairment in adult patients with XLH was evident.

This difference in HRQoL between children and adults with XLH could be explained by two causes. First, measuring HRQoL in children is problematic and therefore the results may not reflect the real quality of life. Concepts of health and disease can differ in children according to their age and cognitive development. Likewise, the effects of the disease and its therapies also differ in children. Accordingly, children may not have the same perception of the consequences and impact of the disease. In addition, EQ-5D questionnaires do not assess factors such as familial relationships or cognitive skills which can modify the quality of life in children. Children also tend to normalize their limitations and have an enormous ability to adapt, so in many cases they remain unaware of their limitations. Thus, whenever possible, it is recommended to use children-specific instruments, as well as disease-specific questionnaires or scales [15]. Unfortunately, there is no specific XLH instrument for children or adults. We did not use a children-specific instrument as we wished to obtain uniform results in children and adults. We chose the EQ-5D instrument because it has been used in other studies on HRQoL in patients with XLH [12] as well as in patients (mainly children) with other rare diseases [16]. Furthermore, the EQ-5D questionnaires are accepted for assessing the HRQoL in children, and the EQ-5D-3L proxy has been considered as a valid instrument [17,18]. And second, XLH by itself can

cause a progressive impact on patient HRQoL and some manifestations are more frequent in adults than in children. Thus, HRQoL in adults is reduced by complications such as deformities, pseudofractures, bone and joint pain, and stiffness of lower extremities [19]. However, many XLH complications in adult patients are thought to be consequences of suboptimal disease management during childhood, as well as inadequate transition to adult health care [8,20,21].

HRQoL impairment in patients with XLH has been found by other researchers. In an international study, the HRQoL of 90 children with XLH was assessed with the 10-Item Short Form Health Survey (SF-10) completed by caregivers or parents. The SF-10 Physical Health Summary score showed impairment in HRQoL with almost 1.5 standard deviations below the norm for the general US population [20]. In adult patients, the EQ-5D-5L questionnaire was used in a similar study of 24 British patients with XLH. Scores were slightly higher than in our adult Spanish patients: mean EQ-5D index and VAS score (using the value set for England) were  $0.648 \pm 0.29$  and  $60.8 \pm 26.9$ , respectively [12], whereas in our series these figures were  $0.562 \pm 0.28$  and  $55.96 \pm 20.86$ , respectively. Reduced HRQoL in adult patients with XLH has been described in other studies, albeit with the use of different assessment instruments. The Health Assessment Questionnaire (HAQ), the Routine Assessment of Patient Index 3 (RAPID3) and the 36-item Short Form Health Survey (SF-36) showed impairment in HRQoL in 52 patients, especially in older individuals and those with structural lesions [11]. HRQoL of patients with XLH was lower than that of patients with axial spondyloarthritis [11], but similar to that of patients with osteogenesis imperfecta or patients with fibrous dysplasia [12]. Both of these diseases affect the musculoskeletal system and can impair mobility because of painful fractures, deformity and chronic pain [22,23]. Additionally, the negative impact of bone and joint pain and functional limitations on the well-being of patients with XLH has previously been demonstrated [24]. Thus, in a recent international study of 232 patients with XLH, pain and functional limitations were the main causes of these patients presenting a HRQoL lower than that of the general population [20].

Among caregivers and parents, the mean EQ-5D-5L index and the mean VAS score were slightly lower than that in general Spanish population. These findings are important, because in the field of rare diseases, the quality of life of caregivers remains under-researched.

HRQoL impairment suggests that conventional treatment with phosphorus and calcitriol, or even recombinant human growth hormone (rhGH), do not prevent the XLH complications that lead to HRQoL impairment in a significant proportion of patients. XLH treatment should ideally act on disease mechanisms and should be able to modify the natural history of the disease [25,26]. Burosumab is an anti-FGF<sub>23</sub> monoclonal antibody that has recently been approved for the treatment of XLH. In clinical studies in children [27] and adults [8,28,29], burosumab increased phosphatemia, improved growth and reduced deformities in children, enhanced physical function, and relieved pain. Recent studies in children [13,30] have confirmed its efficacy and safety. Benefits of burosumab were maintained over 48 weeks [31]. Nevertheless, despite the increase in HRQoL after four months of therapy with burosumab [32], long-term studies are needed to evaluate its efficacy in preventing long-term complications in adults [21]. The information provided by the ongoing International XLH Registry (NCT03193476) will also provide valuable insights into the natural history of the disease and patient response to treatment.

The present study has some limitations. Because of the rarity of XLH we were unable to achieve the target sample size. Thus, due to the small number of patients included, we were unable to analyze as deeply as we would have wished the potential differences in HRQoL by sex or age groups. Another limitation was that there is no specific instrument to assess HRQoL in patients with XLH and we used the generic EQ-5D. As XLH is a variable and heterogeneous disease, the statistical analyses performed may be less accurate than in other diseases, with, for example, larger errors in the mean estimations. A final limitation was that we could not directly compare HRQoL results in pediatric patients and children in the general population due to the lack of data. The last limitation was that the study was conducted before the introduction of burosumab for the treatment of XLH, and thus, estimates of HRQoL in XLH patients may be different in the future.

## Conclusions

HRQoL is reduced in patients with XLH and conventional treatment does not prevent the complications of this disease leading to impairment in the HRQoL of both children and adults.

## Methods

The XLH-QoL project was the result of the collaboration of a committee of XLH experts and a technical team with expertise in the socioeconomic burden of this disease. The aim of the project was to assess the HRQoL of patients with XLH and their caregivers in a multicenter, cross-sectional observational study of pediatric (<18 years) and adult ( $\geq 18$  years) patients diagnosed with XLH, managed in specialized clinics of tertiary hospitals across Spain. All pediatric patients were accompanied by their parents or caregivers.

HRQoL was assessed with the paper-based Spanish version of the EQ-5D instrument [33], which has been validated in the Spanish population [34]. We used the three-level version (EQ-5D-3L) for patients aged between 12 and 18 years, the EQ-5D-3L proxy was completed by parents or caregivers of patients under 12 years, and the five-level version (EQ-5D-5L) was given to adults and caregivers. All questionnaires were anonymous, and no personal data was collected. The study's database was compiled in accordance with the Spanish law on personal data protection (Organic Act 15/1999, of December 13) and the prevailing regulation (Royal Decree 1720/2007, of December 21).

The EQ-5D consists of five questions corresponding to five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and a VAS [35]. The EQ-5D-3L and EQ-5D-3L proxy questionnaires have three possible answers for each dimension, scored from 1 to 3. Similarly, the EQ-5D-5L questionnaire has five possible answers for each dimension, scored from 1 to 5. This is a descriptive system from which a five-digit health state profile is obtained; the profile expresses the level of difficulty experienced in each of the five health dimensions [35]. A weighted overall score (utility index or EQ-5D index) from 0 (death) to 1 (perfect health) can also be obtained, although negative values are allowed for "worse than death" states. The second part of the EQ-5D instrument is a VAS of health status. The scale scores from 0 to 100, where 0 is the worst possible state and 100 the best possible state [35]. We recorded results of the EQ-5D questionnaires in Excel spreadsheets and then we estimated the response percentages for each question as well as the mean and SD for the VAS.

The results were not presented as health profiles but rather as percentages of responses to each option in the five dimensions for pediatric and adult patients. The data collected from the questionnaires was aggregated to estimate the mean  $\pm$  SD for the EQ-5D index and VAS for pediatric and adult patients as well as for caregivers.

We planned to compare our results with those of the general Spanish population according to the ENSE 2017 [36]. However, when this survey was published, we found that it did not collect HRQoL data in adults. We then used the previous ENSE 2011 [14], which utilized the EQ-5D-5L questionnaire to assess HRQoL in adults. Nevertheless, we could not compare HRQoL in children with XLH and the general Spanish population, because 1) ENSE 2011 did not include this assessment [14]; and 2) ENSE 2017 did not use the EQ-5D questionnaires to evaluate HRQoL, but the parent version of the KIDSCREEN-10 questionnaire for children from 8 to 14 years old [36].

## List Of Abbreviations

ENSE, National Health Survey of Spain; EQ-5D-3L, EuroQoL-5 Dimensions-3 Levels; EQ-5D-5L, EuroQoL-5 Dimensions-5 Levels; FGF, fibroblast growth factor; HAQ, Health Assessment Questionnaire; HRQoL, health-related quality of life; RAPID3, Routine Assessment of Patient Index 3; rhGH, recombinant human growth hormone; SD, standard deviation; SF-10, 10-Item Short Form Health Survey; SF-36, 36-item Short Form Health Survey; VAS, visual analogue scale; XLH, X-linked hypophosphatemia.

## Declarations

- Ethics approval and consent to participate

This study was approved and classified by the Spanish Agency for Medicines and Health Products (AEMPS) as a non-interventional observational post-authorization study and was approved by an Ethics Committees for Clinical Research (CEIC; University Hospital Puerta de Hierro Majadahonda) (approval number 18.17). Furthermore, this study has been performed in accordance with the Declaration of Helsinki.

Patients aged 12 to 18 years, adult patients, and caregivers or parents of all pediatric patients were informed verbally and in writing, and informed consent was obtained before participation in the study.

- Consent for publication

Not applicable.

- Availability of data and material

All the data generated or analyzed during this study are included in this article and its supplementary information files.

- Competing interests

MILY, PP, CV, MR-K, JH, JJB, LE, SM, LP-S, VM, CP, JAP, MAC and JE have received lecture fees from Kyowa Kirin Farmacéutica. SM has received lecture fees and advisory *honoraria* from Kyowa Kirin Farmacéutica. GA has received lecture fees and advisory *honoraria* from Kiowa Kirin as well as support to attend scientific meetings. INV and AJ are employees of Kyowa Kirin Farmacéutica. MD-C declares that he has no competing interests.

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- Authors' contributions

All authors participated in this project by conceiving the analysis, collecting the data, and writing and editing the manuscript. All authors approved the manuscript for submission.

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## Table

**Table 1. Quality of life in adults with XLH and in the general Spanish population according to the 2011-2012 National Health Survey [14]. Response percentages in the different dimensions of the EQ-5D-5L questionnaire.**

Dimension	Options	Patients with XLH (%) (n=29)	General population (%) (n=20,587)
Mobility	No problems	6.90	85.72
	Slight problems	37.93	6.25
	Moderate problems	31.03	4.76
	Severe problems	20.69	2.45
	Extreme problems	3.45	0.82
Self-care	No problems	48.28	93.78
	Slight problems	31.03	2.52
	Moderate problems	17.24	1.77
	Severe problems	3.45	0.93
	Extreme problems	0.00	1.01
Usual activities	No problems	20.69	88.86
	Slight problems	34.48	4.87
	Moderate problems	31.03	3.22
	Severe problems	13.79	1.58
	Extreme problems	0.00	1.46
Pain/discomfort	No problems	13.79	75
	Slight problems	10.34	12.51
	Moderate problems	34.48	8.86
	Severe problems	37.93	4
	Extreme problems	3.45	0.41
Anxiety/depression	No problems	34.48	84.97
	Slight problems	31.03	8.6
	Moderate problems	24.14	4.25
	Severe problems	10.34	1.68
	Extreme problems	0.00	0.41

## Additional File Legends

Additional file 1

- File format: Word (.docx).
- Title of data: Table S1. Quality of life in children with X-linked hypophosphatemia (N = 21). Response percentages in the different items of the EQ-5D-3L and EQ-5D-3L proxy questionnaires.
- Description of data: Table with results that complements Figure 1.

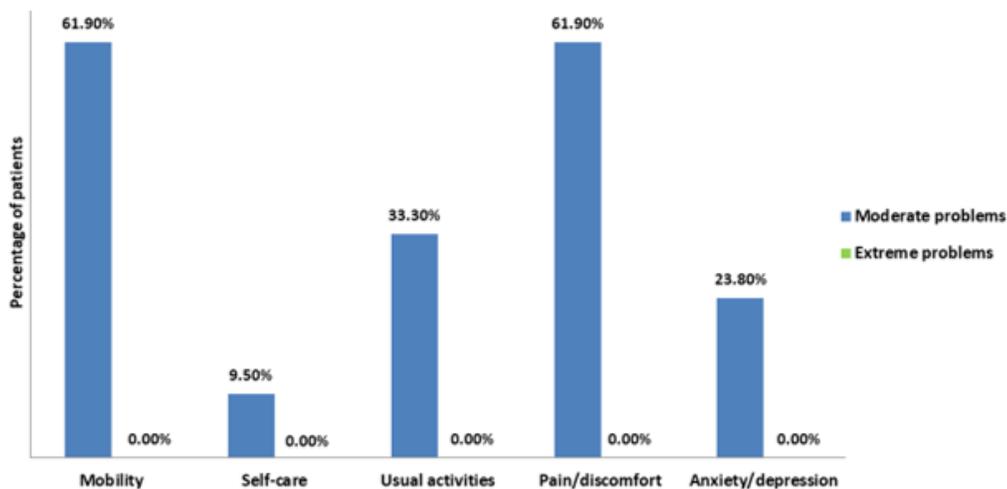
### Additional file 2

- File format: Word (.docx).
- Title of data: Table S2. Quality of life in adults with X-linked hypophosphatemia (N = 29). Response percentages in the different items of the EQ-5D-5L questionnaire.
- Description of data: Table with results that complements Figure 2.

### Additional file 3

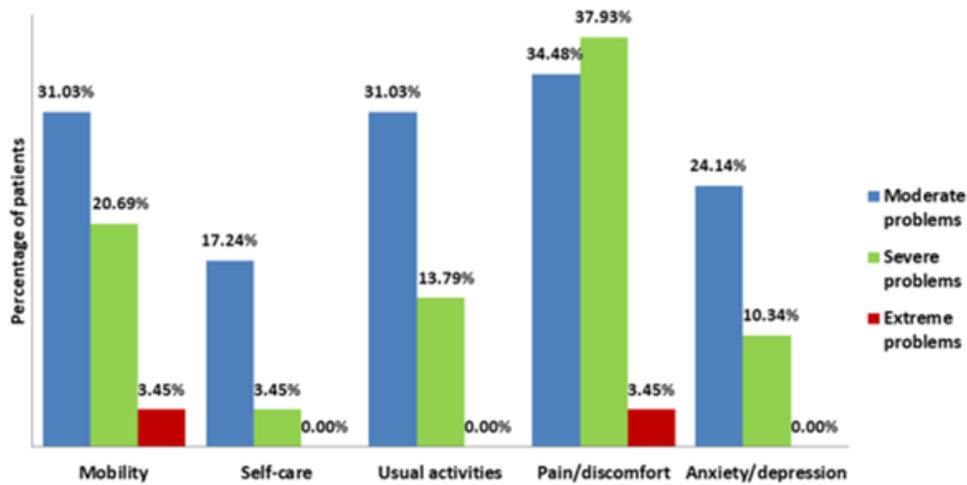
- File format: Word (.docx).
- Title of data: Table S3. Quality of life in caregivers/parents of children with X-linked hypophosphatemia (N = 21). Response percentages in the different items of the EQ-5D-5L questionnaire.
- Description of data: Table with results of quality of life in caregivers and parents.

## Figures



**Figure 1**

Percentages of pediatric patients with X-linked hypophosphatemia (n = 21) with moderate or extreme problems in each dimension of the EQ-5D-3L and EQ-5D-3L proxy questionnaires.



**Figure 2**

Percentages of adult patients with X-linked hypophosphatemia (n = 29) with moderate, severe or extreme problems in each dimension of the EQ-5D-5L questionnaire.

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Additionalfile2.docx](#)
- [Additionalfile3.docx](#)
- [Additionalfile1.docx](#)