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Patient Perspective

Whole Body, Whole Life, Whole Family: Patients' Perspectives on X-Linked Hypophosphatemia

Amber A. Hamilton,[1,2] Susan Faitos,[3] Gin Jones,[4] Athina Kinsley,[5] Rupal Naik Gupta,[6] and E. Michael Lewiecki[7]

[1]Patient advocate, NY, USA
[2]Department of Orthopedic Surgery, Emory University School of Medicine, Atlanta, GA 30322, USA
[3]The XLH Network, Inc., Albany, NY 12206, USA
[4]Patient advocate, MA, USA
[5]Patient advocate, CA, USA
[6]Ultragenyx Pharmaceutical, Inc., Novato, CA 94949, USA
[7]New Mexico Clinical Research & Osteoporosis Center, Albuquerque, NM 87106, USA

Correspondence: E. Michael Lewiecki, MD, New Mexico Clinical Research & Osteoporosis Center, 300 Oak Street NE, Albuquerque, NM 87106, USA. Email: mlewiecki@gmail.com; or Rupal Gupta, PharmD, Ultragenyx Pharmaceutical, Inc., Novato, CA 94949, USA. Email: RGupta@ultragenyx.com.

Abstract

The rare genetic disorder X-linked hypophosphatemia (XLH) is often exclusively considered to impact children, and, as such, adult patients with XLH may receive inadequate care because their symptoms are not associated with XLH. However, studies have shown that XLH has long-term adverse health consequences that continue throughout adulthood requiring comprehensive lifelong care. Indeed, XLH impacts patients' whole body, whole life, and whole family. XLH does not just affect the bones; symptoms are chronic and progressive, worsening throughout adulthood, and the burden of XLH overflows into the lives of a patient's family, friends, peers, and colleagues. To ensure early recognition, comprehensive care, and adequate management of XLH, there are key steps that clinicians can incorporate into their daily practice. These include education, a multidisciplinary approach, open communication, and support. Clinician education on rare disorders such as XLH is critical, and healthcare professionals (HCPs) should ensure that patients and their caregivers have access to XLH-related information. As a whole-body disorder, XLH requires a coordinated approach to treatment across specialties. Frequent open communication among members of the healthcare team is needed to increase HCPs' knowledge about XLH, and open communication must extend to the patient as well to ensure the patient's concerns and needs are addressed and treatment is tailored to their specific individual needs. Multiple networks of support, including social and psychological support, should be offered to patients and their families. A basic understanding that XLH affects patients' whole bodies, whole lives, and whole families is the first step toward accomplishing improved patient care.

Key Words: patient perspective, X-linked hypophosphatemia, XLH

Abbreviations: FGF, fibroblast growth factor; HCP, healthcare professional; *PHEX*, phosphate-regulating endopeptidase homolog X-linked; XLH, X-linked hypophosphatemia.

X-linked hypophosphatemia (XLH) is a rare genetic phosphate-wasting disorder caused by mutations in the phosphate-regulating endopeptidase homolog X-linked (*PHEX*) gene. Loss of *PHEX* function leads to overproduction of hormone fibroblast growth factor 23 (FGF23) [1]. FGF23 is implicated in phosphate metabolism, and high levels of FGF23 result in phosphate wasting by the body, leading to hypophosphatemia [1].

XLH is often viewed exclusively as a childhood bone disorder that is only symptomatic during childhood growth [2]; as a result, adult patients with XLH may receive inadequate care because their symptoms are misdiagnosed as unrelated to XLH. However, recent studies have shown that XLH has long-term adverse health consequences that continue throughout adulthood [1, 2]. For example, low phosphate levels impair the body's ability to mineralize bone causing lower limb deformity, chronic pain, muscle weakness, fatigue, and dental abnormalities (leading to caries and abscesses) in children that persist into adulthood and advance to progressive osteoarthritis, fractures, pseudofractures, joint stiffness, hearing loss, decreased range of motion, and impaired mobility due to widespread calcifications and enthesopathy [1-4].

XLH research has caught significant momentum in the past decade, generating novel treatments. Burosumab, an anti-FGF23 monoclonal antibody [5], has emerged as an efficacious treatment option. Prior to burosumab, electrolyte repletion with multiple doses of phosphate, vitamin D, and vitamin D analogs such as calcitriol were necessary [1]. Nonetheless, the XLH community as a whole would like to enhance clinicians' understanding of the disorder.

Studies show that there is a significant delay in the time to translate research and scientific findings to clinical practice. A literature review of 23 publications that assessed the time delay from bench to practice for a range of clinical conditions approximated the gap as 17 to 23 years [6]. In the case of XLH research, clinical practice recommendations have only been published in recent years despite there being over

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100 XLH-related research articles, case studies, and review articles [7]. The consequences of delay to implementation of knowledge are harmful, progressive, and potentially permanent. For patients with XLH, this time can equate to the entire length of one's childhood or other stage of life.

In this article, we, as patients with XLH, a clinician, and a medical affairs professional, discuss how reliance of clinicians on outdated information adversely impacts lives of patients with XLH. We propose several ways in which healthcare professionals (HCPs) can adjust treatment methodologies to mitigate the burden of XLH on patients and their families.

XLH Triad

XLH is multifaceted, affecting a patient's whole body, whole life, and whole family [2, 4]. As HCPs and presenters at educational symposia, and through interaction with patients, Elizabeth Olear, MS, MA (Yale School of Medicine, New Haven, CT), and Marian Hart, BSN, RN, CCRC (Indiana University School of Medicine, Indianapolis, IN), have worked to define the concept of "whole body, whole life, whole family." Here, we, the authors, explore this concept, drawing on our personal experience plus testimony and data gathered from a symposium presented by the XLH Network, Inc. ("the XLH Network"), a patient support and advocacy group. The XLH triad concept represents a change in the lens through which XLH is viewed that could lead to better management of this lifelong disorder.

Whole Body

XLH affects the entire body, not just the bones. FGF23 overproduction stimulates excessive phosphate excretion via the kidneys, decreases 1,25-dihydroxyvitamin D production, and increases 1,25-dihydroxyvitamin breakdown, all of which synergistically result in hypophosphatemia [1]. Chronic low levels of phosphate in XLH negatively impact bone formation, as well as teeth, muscle/nerve function, hearing, energy levels, and other cellular processes [1]. The misperception that XLH is exclusively a childhood bone disorder can lead to neglect of its broader implications [4].

At the XLH Network's Symposium on Hypophosphatemia: Past, Present, and Future, patients and caregivers reported that XLH wreaks havoc on almost every bodily system, including skeletal, muscular, auditory, and vision [2]. They also reported full-body muscle weakness and "joint pain, muscle pain, . . . fatigue, hearing loss, vertigo attacks or dizziness with brain fog and loss of functional mobility" [2].

When combined with clinicians' unfamiliarity with XLH and underappreciation of its impact on patients, the wide-ranging manifestations of XLH can have devastating consequences. Presentation of XLH may be misinterpreted as psychological in nature, or incorrectly labeled as drug-seeking behavior by some HCPs [2]. The XLH Network's fall 2017 survey results showed that 38% of adult patients reported chronic pain as the symptom having the biggest negative impact on their lives, a higher proportion than for any other symptom. For pediatric patients, chronic pain had the second-greatest negative impact (18%) after lower limb deformities (32%) [2].

Constrained office visit time restricts the clinician from all-inclusive management of the patient with XLH [2]. Clinicians may feel pressured to focus on the most visible XLH symptoms, but they need to be aware that patients are likely to experience additional ongoing XLH-related symptoms. The patient may be reluctant to mention all symptoms and may downplay their severity [2]. Patients may grow accustomed over time to levels of persistent pain, fatigue, and muscle dysfunction that would not be tolerated by others [2]. Some patients have reported that they "didn't know how bad [they] felt" until they finally received an effective treatment [2]. Furthermore, given the complex nature of managing XLH, not all manifestations of the disorder may be handled by the same HCP. This often leads to disorganized communication among those involved [2].

Whole Life

Symptoms of XLH are chronic and progressive. They not only persist but worsen throughout adulthood [1-4]. Patients require a treatment regimen that prevents lower extremity deformities initially and then optimizes bone mineralization throughout life. This can be achieved with frequent follow-up and routine blood draws to assess metabolic status as it pertains to patients' musculoskeletal and renal health. Additionally, childhood deformity correction surgery often requires further procedures as bones grow, due to joint malalignment and wear and tear of poorly mineralized bone [2, 7]. Moreover, additional symptoms present or progress in adulthood, including hearing loss, early-onset arthritis, and widespread calcification of soft tissue [1, 4].

During the XLH Network's symposium, 1 patient described escalating symptom progression that began in her late 20s [2]. Her condition deteriorated from being able to dance, to being in a wheelchair, then a powered wheelchair, to eventually losing the ability to drive a car in her 40s. Now in her 70s, she is unable to pick up a piece of paper or write. She has ongoing chronic pain, weakness, fatigue, and loss of hearing and functional mobility. In the XLH Network's fall 2017 survey (N = 186), 47% of adult patients with XLH scored their childhood symptoms as moderate and 29% as severe. In comparison, 46% scored their adult symptoms as moderate and 46% as severe. This suggests that symptoms not only persist into adulthood, but that they worsen. As symptoms worsen, impact on quality of life increases; 84% of survey respondents said that their worsening XLH symptoms have greatly affected additional areas of their lives over time [2].

Finally, there is a great need for, and distinct lack of, transitional care for adolescent patients as they enter adulthood [2, 3]. This is likely due to scarcity of specialists familiar with XLH in adults and the outdated perception of XLH as a childhood disorder. Indeed, during the XLH Network's symposium, 1 patient expressed a strong desire to see more information for teenagers because there is a lack of education surrounding surgeries, transition from pediatric to adult care, and self-care over time [2].

Whole Family

The burden of XLH overflows into the lives of a patient's family, friends, peers, and colleagues [2]. It may be difficult for others to understand the breadth of physical limitations due to XLH; therefore, education on the disorder should be expanded beyond patients alone. Mobility issues, fatigue, and chronic pain create physical limitations for patients with XLH. This can impair a patient's ability to fully participate in family or social activities [2]. In a live survey during the XLH

Network's symposium, 59% of respondents ranked participation in sports and recreational activities as the most important pursuits that the affected patient used to be able to do but now could not do as well because of XLH progression. Furthermore, 84% of respondents indicated that all areas of life, including home, work, and friendships, were affected by symptom worsening as XLH progressed.

Living with XLH has financial implications. Many patients report inability to continue working due to the physically strenuous demand of their jobs on their bodies [2], and they often have costly medical and dental expenses that may not be covered by insurance.

Finally, young adults with XLH face difficult family-planning decisions. XLH is an inherited disorder with the potential to be passed on to children. Genetic counseling and the option of in vitro fertilization with preimplantation genetic diagnosis are substantial undertakings for these patients. The idea of childbearing and rearing may feel daunting to some patients due to physical demands. Adoption may also not be an option for the same reason. During the XLH Network's symposium, 1 36-year-old with XLH commented on the lack of available education for adults, noting that there is no one to tell them whether "[they] should have children, what [they] can expect, [or] how to take care of [their] bodies" [2]. It is currently unclear how availability of new treatments will impact patients' family-planning decisions.

A Call to Action

After careful discussion and consideration, we have detailed key steps that clinicians can incorporate into their daily practice to ensure early recognition, comprehensive care, and adequate management of XLH.

Education

Clinician and patient education on rare disorders such as XLH is critical. Understandably, all clinicians are not experts in every rare disease. Nonetheless, pediatricians, endocrinologists, and primary care clinicians are likely to be the first to see patients with XLH, so their understanding of the nuances of this particular disorder can aid in its early recognition and comprehensive treatment. This includes awareness that XLH also affects adults and can have a highly heterogeneous presentation. Failure to unite a broad collection of symptoms under an XLH diagnosis results in delayed or incorrect diagnoses and narrow symptomatic treatment [1, 7]. For example, patients may have well-documented chronic symptoms, such as osteoarthritis or calcifications, without clinician recognition that the symptoms are linked to XLH. These patients may be referred for surgical interventions specific to the symptom without consideration of the greater need to understand and treat the XLH [2, 7]. Clinicians new to XLH treatment or working with a patient who has a particularly challenging presentation may find useful resources on the Rare Bone Disease TeleECHO platform, and clinicians with a special interest in XLH are encouraged to participate [8].

Clinicians and other HCPs should also ensure that patients and their caregivers have access to XLH-related information. This includes, but is not limited to, emotional/mental, physical and occupational health resources, and information on support groups. This will help patients to better understand their symptoms and how they might be related to XLH. Patients will then be able to communicate more effectively with clinicians about their symptoms and participate more actively in treatment planning. Clinicians in turn need to be committed to listening to their patients and responding accordingly.

Multidisciplinary Approach

As a whole-body disorder, XLH requires a coordinated approach to treatment across specialties to provide comprehensive care. This includes endocrinologists, nephrologists, orthopedic surgeons, occupational and physical therapists, pain management specialists, dentists, and primary care clinicians. Neurologist, neurosurgeon, orthodontist, and ophthalmologist care may also become necessary, depending on the patient's symptom presentation and needs.

One way to increase HCPs' knowledge about XLH is through frequent, open communication among members of the healthcare team. Additionally, care gaps among specialties can be filled through action of a multidisciplinary team, providing treatment for the entire disorder. This team should also include an expert in transitional care. Using this model, pediatric patients who are typically dismissed at age 18 years can be properly educated and transitioned to adult care [2]. Although the multidisciplinary approach has been suggested before [7], it is seldom followed in clinical practice.

Support

Patients and their families should be offered multiple networks of support. Social workers can help manage challenges of living with XLH and navigate the healthcare system with a rare multisystem disorder. Patients of all ages may need psychological support to help them manage emotional stressors of XLH, such as loss of personal freedom, social isolation, disabling pain, and progressing symptoms. Additional life issues, such as loss of jobs and careers, financial uncertainty, and family issues, may also arise, and their impact may be amplified by the additional burden of living with a chronic illness.

Open Communication

Wellbeing of patients is the ultimate goal. To ensure that all of a patient's concerns and needs are addressed, open communication among multidisciplinary team members must extend to the patient as well. Open communication between clinicians and patients will help tailor treatment to specific individual needs and ensure that all treatment options are explored and employed effectively. This is particularly important in a multisystem disorder such as XLH because no 2 patients, even patients within the same family, will experience the same combination and severity of symptoms. When asked the top 2 XLH-related symptoms that impact quality of life, patients participating in a survey at the XLH Network's symposium were split among joint stiffness (30%), fatigue (23%), and bone pain (22%), with dental abscesses (14%) and muscle pain (11%) not far behind [2]. This highlights the heterogeneity in patients' experiences.

The healthcare team is tasked with taking a careful attentive history from patients with XLH. Understanding the scope of patient concerns can be difficult, particularly with symptoms such as chronic pain and fatigue because they are often not overtly apparent and are therefore underappreciated. Only

through listening to and believing patients can clinicians and patients work together to treat the full range of XLH symptoms.

Conclusion

We have identified several key steps that we believe will assist clinicians in providing comprehensive care when treating this disorder. It will take time for clinicians to incorporate these ideas into daily practice and to better understand XLH from the patient perspective. Additionally, not every clinician can become an expert in every rare disease. Nonetheless, a basic understanding of XLH as affecting patients' whole bodies, whole lives, and whole families is the first step toward accomplishing improved patient care.

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Additional resources for patients with XLH and clinicians can be found on the XLH Network website: https://www.xlhnetwork.org/xlh-resources and also on the International XLH Alliance's resource page: https://xlhalliance.org/resources/. For clinicians, reference 7 provides comprehensive clinical practice recommendations for the diagnosis of XLH, including evaluations of common and rare complications.

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Data Availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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