The unrecognized burden of XLH in adults

A call to action

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Foreword

On behalf of the International XLH Alliance, we are delighted to be able to introduce this critical piece of work on the unmet needs of adults with X-linked hypophosphataemia (XLH).

The International XLH Alliance aims to amplify the patient voice for those with XLH and related disorders, to set a global multidisciplinary standard for care and research that could not be achieved independently, to ensure that management for all patients is the same.

For us the development of this White Paper is important as it will stimulate discussion of the issues that need to be addressed around care for adults with XLH.

Today, awareness of the impact that XLH has during adult life is sadly very low. In particular, our members notice a lack of awareness among healthcare professionals of the need for ongoing specialist care in adulthood, and the importance of the involvement of a wide range of specialists. This represents a major challenge for us as individuals living with the disease and needs to be addressed.

When shaping the healthcare agenda, it is important that policymakers, healthcare funders and organizers and other stakeholders are aware of the issues that matter most to people living with XLH. We hope that this White Paper will help to start a conversation that will lead to improved XLH care.

Oliver Gardiner and Tia Haverinen

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XLH UK and Kalfos ry are members of the International XLH Alliance, a collaborative network of national patient groups from around the world that provides a single global voice for patients with XLH and related disorders.

Contents

Introduction

X-linked hypophosphataemia (XLH) is a rare and life-long disease. It is the most common form of hereditary rickets.[1] The disease causes a broad range of medical issues, including metabolic, skeletal, muscular, sensory and dental problems, which can progress over time.[1-4] A recent study even suggests that individuals with XLH may have shorter life expectancies than people without the disease.[5] It is often inherited from a parent, although in many cases there is no family history of the disease.[6,7] As is the case for many rare diseases, timely diagnosis can be challenging and delays are common.[8]

Signs and symptoms of XLH usually begin in infancy, with children experiencing delayed walking, painful bone deformities and poor growth leading to short stature.[1,2,9] Historically, it was thought that XLH was solely a childhood disease and that most symptoms would go away upon reaching adulthood.[10] It is now clear that in adulthood people with XLH continue to experience a spectrum of chronic symptoms throughout the body that result in a progressive loss of physical function and represent a considerable burden for the individual, their family, society and the healthcare system.[3,4] Therefore, a life-long approach to the management of XLH is needed.

For the past 40 years, XLH has been managed during childhood, and in some cases in adulthood, using activated vitamin D and phosphate supplementation.[1,9] However, this conventional therapy does not fully address the needs of children or adults with XLH.[1,3]

Greater understanding of the challenges faced by adults with XLH is essential in order to be able to give people with this condition the high-quality care that they deserve, which is why this White Paper has been developed.

Methodology

This White Paper examines, analyses and discusses evidence available on the burden associated with XLH in adulthood, including the impact on the individual, their family, society and the healthcare system. Scientific sources have been identified through a systematic review of the medical literature,[11] with additional sources recommended by the authors and the International XLH Alliance.[10,12-14] Interviews with adults with XLH and clinicians involved in their care provide personal and clinical perspectives of XLH from within Europe. A survey of Patient Group Leaders from organizations in 11 European countries prioritizes key unmet needs from those found in the literature review. This paper evaluates and draws together these findings to formulate a call to action that suggests how care for adults with XLH can be improved.

What is XLH?

XLH is a debilitating disease that has life-long consequences.

The disease develops because of mutations in one of the genes on the X-chromosome known as the *PHEX* gene.[1] As a result, levels of a hormone responsible for regulating the level of phosphate in the blood are much higher than they should normally be.[2] This leads to excessive loss of phosphate in the urine and low levels in the blood, which is known as hypophosphataemia.

Phosphate is a mineral that is essential for multiple physiological processes including the maintenance of healthy bones, muscles and teeth. Lack of phosphate leads to the progressive development of the incapacitating signs and symptoms characteristically experienced by people with XLH.[1,2]

In adults with XLH, the skeleton, muscles, nerves and teeth are all affected by the lack of phosphate, and individuals experience pain and mobility issues which profoundly impact their quality of life.[10]

1. XLH – a disease with substantial life-long burden

Clinical burden of XLH in adulthood

Adults with XLH experience a wide range of debilitating symptoms affecting most areas of the body (**Figure 1**).[3] People with XLH tend to be short in stature. Impaired skeletal development during childhood leads to characteristic features, such as bowed legs, that persist into adulthood.[3,15-17] Bones remain misshapen and weak in adulthood, and adults with XLH therefore experience a range of skeletal problems including fractures and pseudofractures.[1] Further manifestations experienced by adults with XLH include early onset arthritis, joint stiffness, musculoskeletal pain, muscle weakness and fatigue.[3,4,17-19] Taken together, these problems place limitations on physical ability and activities of daily life.[3,17-19] Many individuals experience progressive deterioration of physical function and ultimately most adults will have severely restricted mobility.[10,20]

Personal perspective

My 30s have been really challenging for me. All my problems started more-or-less simultaneously when I was 28 years old. I began having dental issues and a lot more bone pain and muscle weakness. It got to the point when I was 35 or 36 years old, where there were days that I couldn't even walk without massive amounts of pain. Some days I would just sit down and feel miserable, thinking that maybe I would never be able to walk again."

– Adult with XLH, Finland.

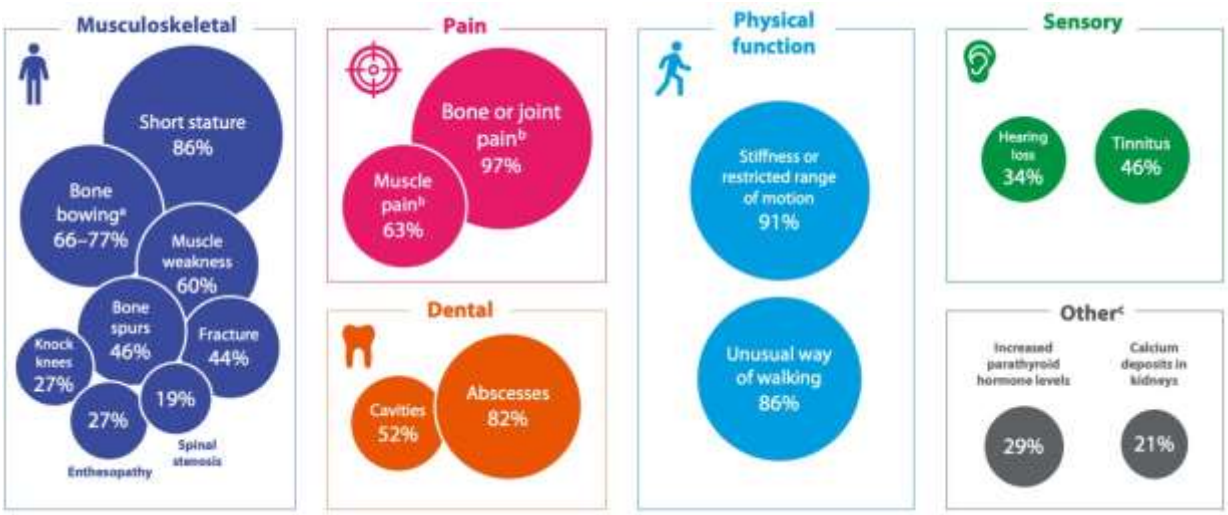

Figure 1. Proportion of adults who reported experiencing signs and symptoms associated with XLH.

Data shown are from the largest published study on burden of disease in adults with XLH (n = 232).[3]

[a]66% of adults experienced bowing of the thigh bone; 77% experienced bowing of the long bones of the lower leg. [b]Pain experienced in the year prior to participating in the survey. [c]Conditions thought to be related to use of vitamin D and phosphate-replacement therapies.

Early onset osteoarthritis is a common finding in adults with XLH which arises, not only as a long-term consequence of weight bearing on misaligned hips, knees and ankles, but also owing to disease-associated disturbances of cartilage formation.[21] Osteoarthritis is associated with the formation of bone spurs (bony lumps around the joints or on the spine), joint pain and spinal stenosis (narrowing of the spinal canal).[3,18,20,22,23] Pain at places where tendons and ligaments connect to the bones (enthesopathy), joint stiffness and muscle weakness further contribute to difficulties in walking and restricted range of joint motion in adults with XLH.[3,15,17,18,20,22,24,25]

Clinical perspective

Adults with XLH have skeletons that are not well aligned and bones that are not properly straight, and it is very difficult to address this with medical care. There is also ongoing pathology in adulthood. Major effects are related to early arthritis – to early wear and tear on the skeleton – and in the most part to early degenerative joint disease, which can be very disabling. On top of this, there are soft tissue complications [affecting the tendons, ligaments and connective tissue] that lead to stiffness and pain. These things exacerbate each other."

– Doctor specializing in Bone Metabolism, UK.

Sensory defects, including numbness, abnormal sensations on the skin, loss of hearing, loss of balance and tinnitus are also common in adults with XLH.[3,4,17,26]

Dental problems, resulting from poor mineralization of teeth and gum disease, are frequent, and occur despite good oral hygiene; these include an increased risk of abscesses, inflammation and tooth decay.[3,4,15,17,20,24,27-29] Adults with XLH therefore require numerous dental procedures throughout their lives, including root canal surgery and tooth extractions, and suffer a high rate of tooth loss.[1,8]

The substantial clinical burden in adults with XLH is compounded by the need for surgical procedures; adults with XLH typically undergo multiple orthopaedic surgeries to repair fractures, replace knee and hip joints and manage other skeletal complications.[3,22]

Personal perspective

My personal experience includes requiring 18+ surgeries to correct bone abnormalities, as well as requiring multiple restorative dental treatments from having 15+ dental abscesses all over a period of 30 years. I'm now paying the price of having those surgeries as my bones do not heal well."

– Representative with XLH from the Brittle Bone Society, UK.[14]

Clinical perspective

Because they have a disease that affects the teeth in a major way, it is very important that adults with XLH get specialist dental care rather than standard community dental care. To the non-expert, the problems adults with XLH have with their teeth can be addressed by ordinary dental care. They get accused of not brushing their teeth properly, which just isn't the case at all."

– Doctor specializing in Bone Metabolism, UK.

Daily living and quality of life are impaired by XLH

Daily life is restricted by XLH

XLH has a major impact on the day-to-day lives of adults with the disease, both in and out of the home.[10,17,30,31] This is not surprising given that chronic musculoskeletal pain is a consistent feature of the disease in adulthood, impairing mobility and restricting physical function.[10,22,32] In a 2018 survey of 186 adults with XLH, chronic pain and mobility issues were identified as the manifestations of XLH that have the most significant impact on daily life.[10] The chronic pain experienced by affected individuals is often disabling and can interfere with daily activities, even when managed with regular over-the-counter and prescription pain medication.[3,10]

Clinical perspective

All of my patients experience pain. Most of them need analgesic treatment every day."

– Rheumatologist, Spain.

Personal perspective

I have trouble sleeping because I have a lot of pain. I have pain in the lower back, and also in the knees and ankles. When you suffer a lot of pain you are sad and frustrated because you want to do things that you can't do because of the pain."

– Adult with XLH, Spain.

Many adults with XLH require modifications within their home, and use walking aids or other special equipment to improve their mobility.[3,17] Being short can make activities that other people take for granted, such as driving or reaching things around the house, much more difficult for people with XLH. More than half of 18 adults interviewed about their experience of XLH as part of a 2018 research study, reported that their ability to perform activities of daily living including housework, getting dressed, exercising and going shopping was affected.[17]

Personal perspective

My husband helps me with simple things like putting shoes and boots on. If I have Velcro on the shoe then I can do that myself, but I don't always want to go out in shoes with Velcro on them. These little things really mean a lot, I think if anybody with XLH was living on their own then it would be much harder. I have to pay somebody to do my feet, to do my nails and things, because I physically can't reach them, I can't bend to get to them. Aside from the fact that it's really important to look after your feet, obviously as a woman you want them to look nice so not only is it physically important, it is also a mental well-being thing – if you don't have these things done then you don't feel good about yourself."

– Adult with XLH, UK.

The need for adults with XLH to attend multiple appointments with different doctors, dentists and other specialists on a regular basis is also disruptive to both home and work life. Furthermore, XLH affects the ability to work,[10,17,24] with unemployment and early retirement more frequent amongst adults with XLH than in the general population.[33]

Living with and addressing these issues places a financial burden on people with XLH and their families. When asked how XLH affected their adult lives, participants at an international patient group meeting noted that they faced challenges with employment, as well as finding the time and money needed for their frequent visits to healthcare professionals.[13]

Personal perspective

I feel that XLH limits my possibilities at work and stops me realizing my dreams. Fear of what is going to happen to me tomorrow affects my career decisions. For example, I miss a lot of days of work for dental appointments because I can have spontaneous abscesses even though I take really good care of my teeth. So, if I got a new job, I would worry about what my new employer would think if I had to go to the dentist on my first day. It's like a mental game that is always going on in the back of your mind, I'm constantly thinking about how XLH will affect this and that."

– Adult with XLH, Finland.

Impact of living with XLH on emotional well-being and family life

Living with XLH has an adverse impact on emotional well-being, and adults with the disease often experience feelings of sadness or depression, owing to the pain and physical limitations that they experience.[17,31] Coping with the physical symptoms of XLH in adulthood, such as short stature, skeletal deformities and walking abnormalities, has been reported to be associated with low self-confidence and bullying.[31]

Uncertainty about the future, health issues and financial challenges may also affect emotional well-being, and were raised by adults with XLH at an international patient group meeting as key issues affecting their lives.[13] Deciding whether or not to have children is a particular concern for adults with XLH owing to the high likelihood of passing the disease to their children, as well as the physical demands of pregnancy and parenthood.[10,31,33,34] In addition, some individuals have grown up with older relatives with XLH and witnessed their deteriorating health, adding to fears about their own future and the impact their condition will have on their own families.[10,31]

XLH does not just affect the individuals with the disease themselves, but also their family and friends, who are often involved in their support and care. When asked about what extra support is needed but lacking, adults with XLH at the international patient group meeting suggested mental health support, family planning, physical therapy and support networks,[13] highlighting a current lack of care in these areas.

Personal perspective

I'm afraid that things might get worse as I get older. There are symptoms I now experience that 10 years ago I didn't know were associated with XLH, and I'm really worried that in 10 years' time the situation might be a lot worse than it is now. Not a day goes by without me thinking and worrying about XLH and the damage that is occurring in my body. I also decided not to have children because of how bad having XLH has been for me – I wouldn't want my children to go through that. It was a really big decision for me and my husband because we really wanted children."

– Adult with XLH, Finland.

Adults with XLH experience poor health-related quality of life

XLH has a substantial and wide-ranging negative impact on health-related quality of life – a formal measure of well-being that includes physical, psychological and social aspects (**Figure 2**).[3,18,19,22,35] Health-related quality of life deteriorates with increasing age, owing to the accumulation and worsening of XLH-related symptoms, in combination with the normal effects of aging.[18,30]

Figure 2. XLH impairs health-related quality of life.

Data shown are from the largest published study on health-related quality of life in adults with XLH (n = 232).[3]

[a]Health-related quality of life was assessed using the 36-Item Short Form Health Survey (SF-36v2); data shown are percentage difference to the general population average in the physical component summary and mental component summary scores. [b]This difference is more than one standard deviation below the general population average and is therefore considered clinically meaningful.

Economic burden associated with XLH in adults

XLH in adulthood is associated with both direct and indirect costs to the healthcare system, society, and affected individuals and their families (**Figure 3**). To date, the economic burden associated with XLH in adulthood has not been calculated; however, the chronic and progressive nature of the condition results in frequent interactions with the healthcare system, and an ongoing requirement for healthcare resources. Adults with XLH should be assessed regularly at the cost of healthcare providers.[1,8,9] In addition to needing frequent surgical procedures, around 70% of adults with XLH require regular pain medication, with as many as 20% taking opioids.[3,22,36] In addition, many require assistive devices to aid mobility.[3,17,36-41]

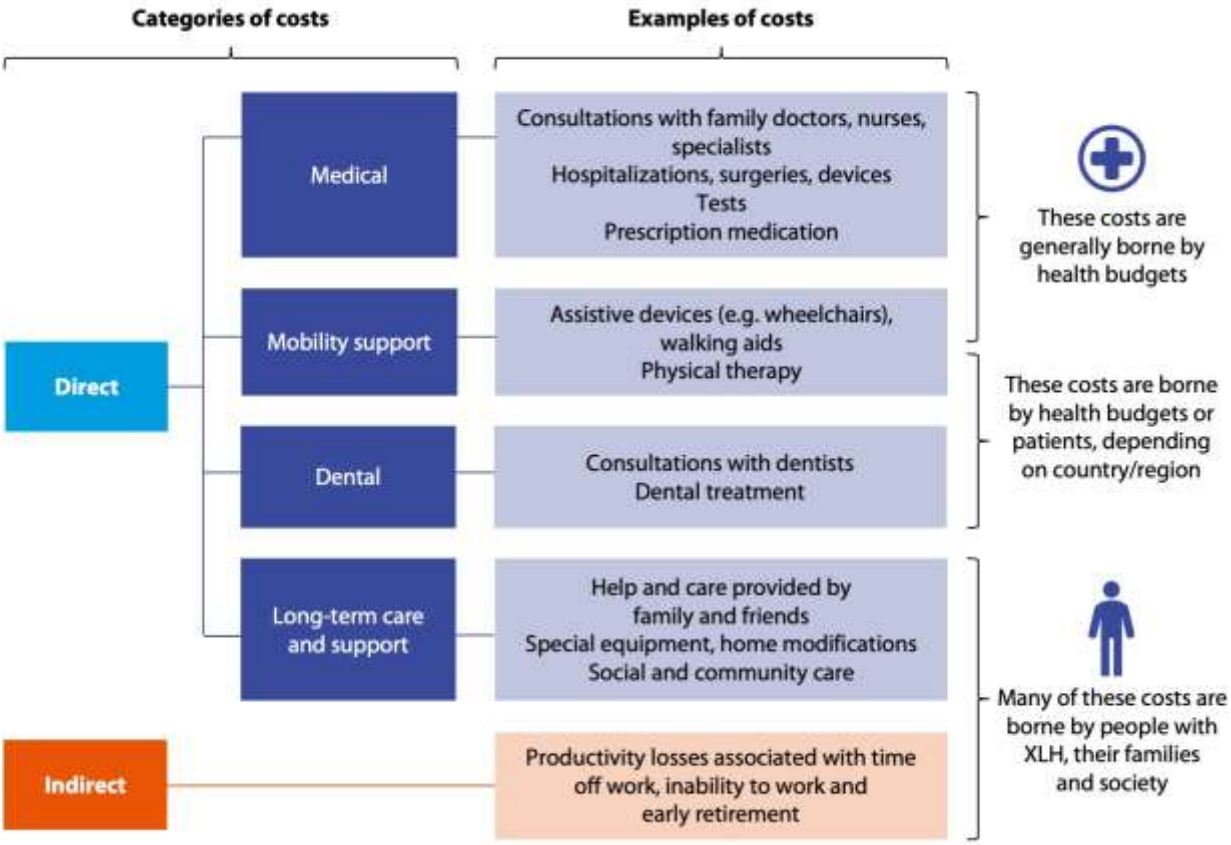

Figure 3. Costs associated with XLH in adulthood.

Special equipment, home modifications and help around the house are often needed as adults with XLH get older and have increasing problems performing daily activities.[17] People with XLH may also require hearing aids.[4] Use of over-the-counter pain medication,[3,22,36,42] and a frequent need for dental treatment including implants and protheses,[43] place additional financial pressure on adults with XLH and their families, and in some countries on the healthcare system. In the UK for example, specialist dental care for XLH at dental hospitals is covered by the National Health Service;[44] although, in some areas adults may not get access to this level of dental care.[32]

Personal perspective

I have tried and tried and tried to see a specialist dentist, but they won't take me on their books. I don't know why. I actually have a terrible fear of dentists – I'd rather go into hospital and have a hip replacement than go to the dentist, because I've had terrible experiences in the past. Even today, I'm sure my local dentist doesn't understand XLH or that my teeth are in such a bad state because of the disease, he just thinks that I don't look after them."

– Adult with XLH, UK.

The impact of XLH on the employment and work life of adults with the disease also has broader societal implications, with productivity losses potentially associated with unemployment, time off from work and early retirement.

Clinical perspective

This is a group of patients who – despite having significant skeletal and dental disease – are still economically active. Most have jobs; they are productive members of society. But as time goes on, there is no doubt that because of premature bone and joint disease they need ongoing medical interventions, so there is an associated medical cost, and this leads to people having to take time off work, or not being able to do their jobs anymore. So, there is a wider societal, economic cost to bear."

– Doctor specializing in Bone Metabolism, UK.

2. Importance of continuity of care

Young adults with XLH deserve a better transition to adult care

Young adults with XLH need to have access to the latest information about their condition and how to manage it, so that they can be actively involved in decision making about their care and treatment. This includes information on how their signs and symptoms may change as they get older. People with XLH often have fairly active childhoods (for example, participating in competitive sports at school) and can be unaware of the impact that XLH will have on their adult lives.[10] This may contribute to a reluctance to receive care on reaching adulthood.[9,10,45]

Awareness of the life-long impact of XLH is particularly important during the transition from paediatric to adult services, when care considerations are changing, and young adults are making important family and career decisions. At this time, aspects of care such as psychological support and genetic counselling may be particularly relevant.[8] However, little information is available to support individuals with XLH as they navigate this critical period of their lives.[10]

Clinical perspectives

Patients in their 30s often feel that they don't need any treatment and refuse to come to the doctor. In this specific time period, it is really difficult to make them understand that treatment and control now, while they are younger, will likely reduce complications that might develop later in life."

– Rheumatologist, Spain.

You certainly see patients who were lost to follow up after paediatric care coming back in with problems later on. We need to try to avoid this by making sure there is lifelong care for genetic conditions."

– Doctor specializing in Bone Metabolism, UK.

Adults with XLH require ongoing, multidisciplinary care

Adults with XLH require regular follow up, and should receive life-long care from a coordinated, multidisciplinary team (**Figure 4**).[8,33] The need for regular monitoring, surgical procedures and physical therapy are central to the clinical management of adults with XLH.[8] The clinical features of XLH in adulthood are wide-ranging, and consequently, pain management, mental health support and genetic counselling, among others, are important considerations in the care of adults with the disease.[8]

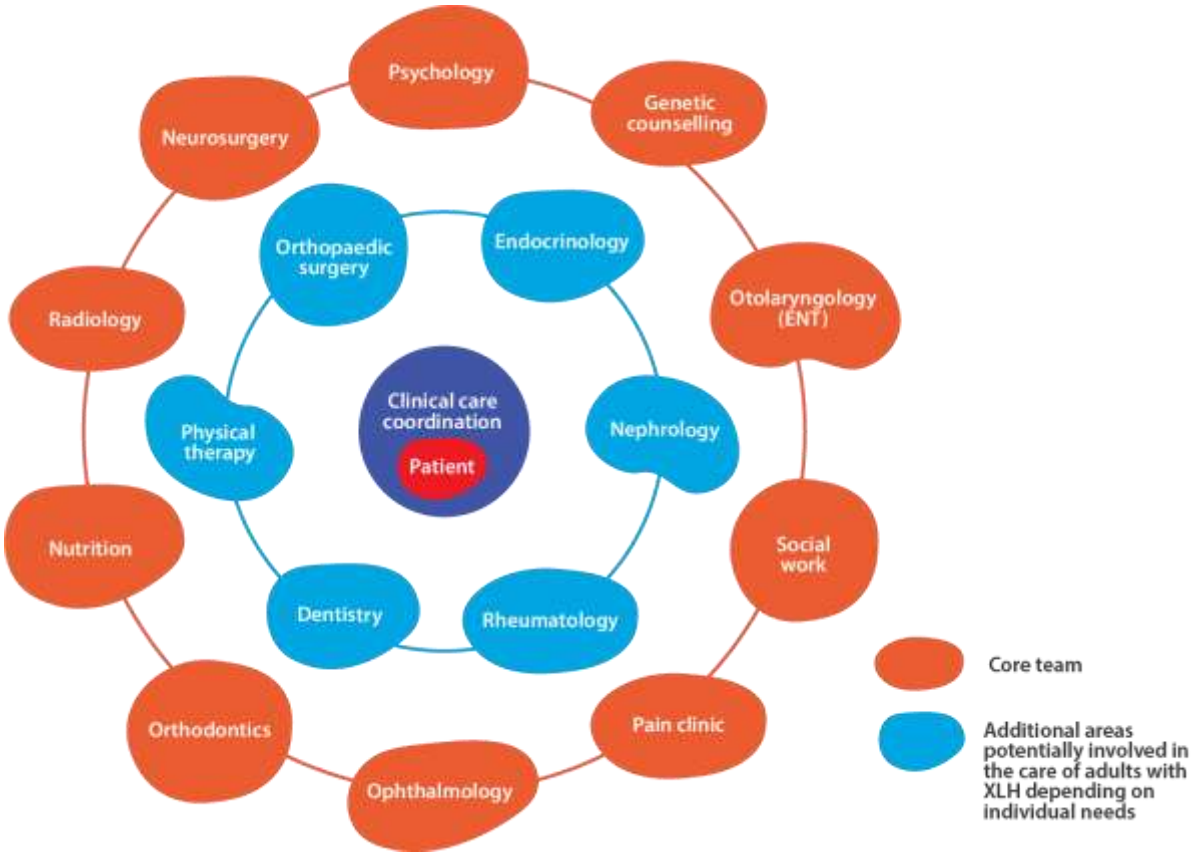

Figure 4. Care of adults with XLH should ideally involve a coordinated, multidisciplinary team of specialists.

ENT, ear, nose and throat.

It is important for healthcare professionals to be aware of the progressive and variable effects of XLH and to provide care tailored to individual needs.[8] However, owing to the rarity of XLH and the medical focus on the disease in children, healthcare professionals outside of specialist centres receive little training on XLH.[8,45] It can therefore be difficult for adults to find specialists who are familiar with XLH and have previously treated someone with the disease.[10]

Personal perspective

My family doctor doesn't know much about XLH and is not interested, so he's never referred me to any other specialists such as dentists or physiotherapists. I feel very frustrated because my doctors aren't really interested in my experience or my suffering, and it makes me feel powerless."

– Adult with XLH, Spain.

3. How can the lives of adults with XLH be improved?

XLH is not simply a childhood growth disorder, but is associated with progressive, debilitating, multisystemic symptoms in adulthood that impact on physical health and emotional well-being. As highlighted earlier in this White Paper, chronic pain, in particular, has a major impact on activities of daily life. A lack of awareness of the condition, ongoing disease complications causing pain and reduced mobility, and the emotional, social and financial impacts of living with a hereditary, chronic disorder all contribute to the burden of XLH in adulthood (**Figure 5**).

Personal perspective

I feel I have to educate the healthcare professionals, which is really frustrating and makes me sad and angry. I can never go to the doctor and just trust that they know what's best for me, that they are the expert and they will tell me how to take care of my disease, because that never happens. I always have to be the one who knows about my disease."

– Adult with XLH, Finland.

Clinical perspective

It is hard when you have a rare disease which is not fully understood. It is logical that patients with XLH should receive some economic support, but when I apply for them to get handicap parking places, or dental care, it is usually denied. There is a lack of understanding about the suffering of those with the disease and how it is hard for them to do things. For example, I have a patient who needs assistance just to get things in the kitchen because he is short. He needs to stand on a stool to get to the high shelf of the cupboard. This would be easy for you and me to do, but people with XLH need help with this kind of small stuff. It affects their lives and their quality of life. It is important to improve knowledge within the healthcare system about the disease and how much it affects patients."

– Doctor specializing in Bone Metabolism, Sweden.

Figure 5. Factors contributing to the burden of XLH in adulthood.

Despite evidence of the substantial burden associated with XLH in adulthood, longitudinal studies in adults with XLH are still scarce in the scientific literature. Research into XLH in adulthood is urgently needed, to better understand the disease burden and changes in needs over time in order to support optimal management. To build on the current evidence base, long-term research including patient-reported outcomes should be encouraged and funded, as well as studies exploring the healthcare and societal burden of XLH in adults.

As well as improving scientific and clinical understanding of XLH in adulthood, urgent action is needed to address the unmet needs of adults with XLH. When asked to prioritize unmet needs, Patient Group Leaders from National Patient Organizations in 11 European countries rated the top unmet need of adults with XLH in their country as referral to adult services, awareness among healthcare providers, coordination of care or access to physiotherapy (**Figure 6**).

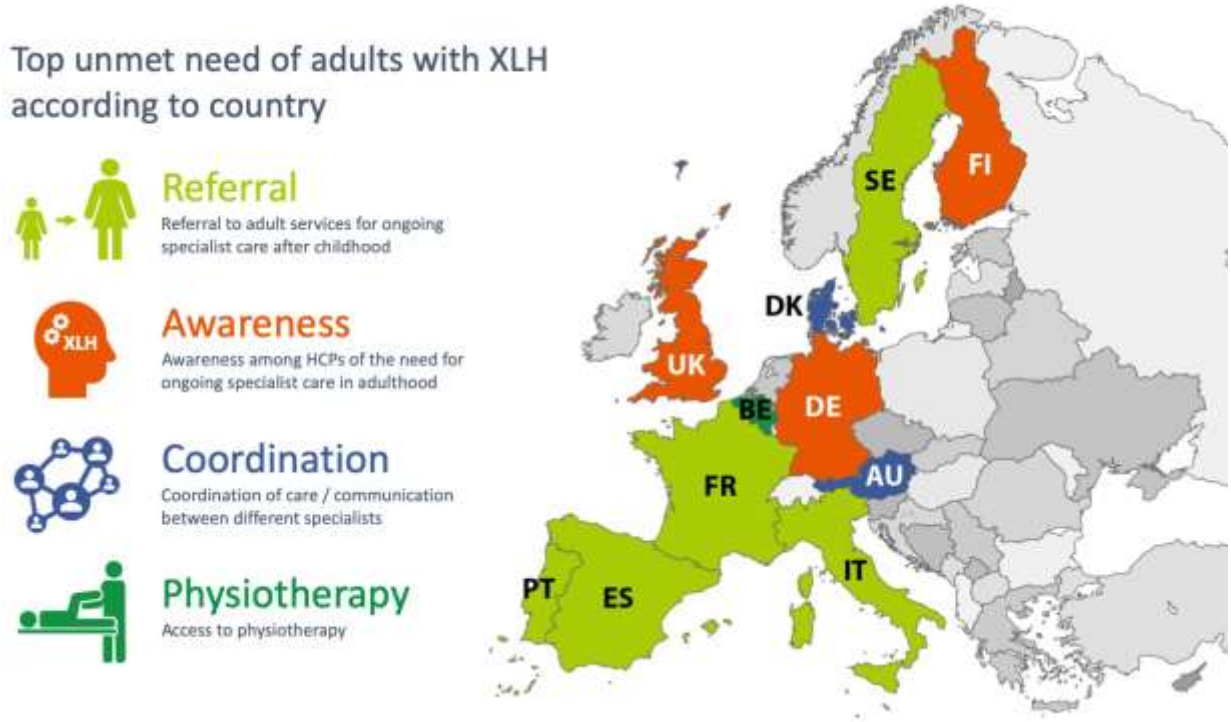

Figure 6. Survey of Patient Group Leaders from XLH National Patient Organizations.

Details of the survey methodology are provided on page 20.

AU, Austria; BE, Belgium; DE, Germany; DK, Denmark; ES, Spain; FI, Finland; FR, France; IT, Italy; PT, Portugal; SE, Sweden.

Clinical perspective

We can improve the care of adults with XLH by working in multidisciplinary teams that include endocrine doctors, orthopaedic surgeons, dentists, nurses and physiotherapists. It is very important in this rare, multisystemic disease that this group of specialists meet, collaborate and discuss the care of the patient. This is a more effective way of working and could improve the care of adults with XLH."

– Doctor specializing in Bone Metabolism, Sweden.

A high need for improved awareness of XLH in adults among healthcare professionals, as well as better access to information for patients about XLH in adulthood were identified by all the groups who participated in the survey. In addition, Patient Group Leaders from several countries highlighted the importance of improving access to and awareness of disability rights and social benefits for adults with XLH.

4. A call to action: changes needed to improve the lives of adults with XLH

XLH in adulthood is associated with substantial burden. Action needs to be taken to improve the lives of adults with the disease and to ensure they have timely and affordable access to the care they need.

Patient organizations play a key role in raising awareness of XLH. Their involvement, alongside that of healthcare professionals, is central to ensuring the XLH community is aware of their rights to education, care and support. **Policymakers need to work to ensure**:

- Adults with XLH receive **ongoing, individualized care from multidisciplinary teams**, including medical, dental and support services
- Implementation of ICD-11, **recognizing XLH, as well as chronic pain** (which is often experienced by adults with XLH), **as conditions in their own right**, in every country in Europe
- Every country has at least **one specialist centre with expert knowledge of XLH**, and that all adults with the disease have the right to access specialized care
- Adults living with XLH have **the right to be recognised as disabled**, thereby guaranteeing access to appropriate equipment/adaptations in the workplace and home, as well opportunities for flexible working
- **EU and national level funding for:**
    - **research into the lifelong individual and societal burden of XLH in adulthood, and**
    - **disease awareness efforts focused towards the wider care community**.

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Survey methodology

A total of 12 National Patient Organizations in Austria, Belgium, Denmark, Finland, France, Germany, Italy (two Italian groups provided a single response), Portugal, Spain, Sweden and the UK were surveyed in August and September 2019.

Patient Group Leaders were asked to rate the level of need for improvements (as high, moderate, low, already satisfied or not applicable) in areas relating to XLH in adulthood (see table), and to rank the top 5 needs in their country. Organizations were able to add to the list of needs, as appropriate.

Needs included in survey (identified in the research for this White Paper)
Referral to adult services for ongoing specialist care after childhood
Awareness among young adults with XLH of the long-term impact of the condition
Obtaining information on XLH during adulthood
Awareness among healthcare professionals of the need for ongoing specialist care in adulthood
Continued access to treatment in adulthood to reduce serious complications
Access to appropriate pain management
Access to counselling and/or mental health support
Access to physiotherapy
Coordination of care / communication between different specialists
Obtaining information about how to manage your condition later in adulthood
Coping with extra costs associated with your condition
Obtaining support from local authorities for home modifications / equipment to aid mobility
Awareness of XLH among the general public
Awareness of XLH among employers
Obtaining support for coping with impaired mobility in the workplace

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