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Review

X-Linked Hypophosphatemia Transition and Team Management

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Abstract: X-linked hypophosphatemia (XLH) is the most common form of inherited disorders that are characterized by renal phosphate wasting, but it is a rare chronic disease. XLH presents in multisystemic organs, not only in childhood, but also in adulthood. Multidisciplinary team management is necessary for the care of patients with XLH. Although XLH has often been perceived as a childhood disease, recent studies have demonstrated that it is a long-term and progressive disease throughout adulthood. In the past 20 years, the importance of the transition from pediatric care to adult care for patient outcomes in adulthood in many pediatric onset diseases has been increasingly recognized. This review describes transitional care and team management for patients with XLH.

Keywords: X-linked hypophosphatemia; transition; team management; transfer

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1. Introduction

X-linked hypophosphatemia (XLH) is the most common form of inherited disorders that are characterized by renal phosphate wasting. XLH presents with a number of symptoms, not only in childhood, but also in adulthood. Despite the long-term and progressive disease burden continuing to adulthood, XLH is often perceived as a rare childhood disease [1–3]. A lack of recognition of the symptoms and signs of XLH in adulthood delays adequate intervention. Although the clinical manifestations of XLH may persist or recur in later life, standard clinical practice involves the discontinuation of conventional treatment when skeletal growth is completed. This is due to limited evidence for the benefits of continuing conventional treatment into adulthood [3,4]. The resumption of treatment based on symptoms results in gaps in care. Seamless follow-ups are needed. Moreover, since XLH presents in a number of organs, the multidisciplinary management of patients with XLH is essential to improve health outcomes. Therefore, appropriate transition is critical for patients with XLH. This review describes transitional care and team management for patients with XLH.

2. Team Management

XLH is a multisystem disorder with musculoskeletal and non-musculoskeletal complications (Table 1). The musculoskeletal complications of XLH include rickets, impaired growth, bone deformities, osteomalacia, bone pain, pseudofractures, enthesopathies, osteoarthritis, dental abscesses, muscle weakness, and gait abnormalities [5–7]. Non-musculoskeletal symptoms include delayed motor development, Chiari malformation, a diminished quality of life, and hearing loss. Several manifestations are more specific to either children or adults. Growth retardation, craniosynostosis, rickets, and delayed motor development are observed in children with XLH, whereas pseudofractures, osteoarthritis, extraosseous calcification—including enthesopathy and spinal stenosis, hearing loss, and disability appear in adulthood. Clinical practice recommendations for the diagnosis and management of XLH advocate regular check-ups for patients by multidisciplinary teams which are organized by an expert in metabolic bone disorders [1,5]. Several excellent studies on the management of XLH have recently been published [8–15]. Since clinical, biochemical, and radiographic features vary between individuals, monitoring and treatment need to

be personalized based on a patient's clinical manifestations, medical history, and stage of development [5,16]. Recommendations for follow-ups, the treatment and management of orthopedic conditions, dental health, hearing, and neurosurgical complications in patients with XLH have been described in detail and summarized [5]. XLH management goals have been summarized as follows: initiate and continue medical therapy; prevent and resolve rickets with early treatment; minimize the risk of developing skeletal deformities; monitor and improve growth and growth velocity; use guided growth procedures; ensure an understanding of therapies and self-administration; psychological, psychosocial, and mental well-being support; ongoing dental care; ongoing physical activity; healthy lifestyle and mobility; the ability to navigate healthcare and insurance systems; corrective surgeries as indicated; therapy self-administration; reproductive health; knowledge of XLH risks and symptoms; self-advocacy; education about therapies, including new developments; monitoring for spinal stenosis and enthesopathy; resolving pseudofractures; and preventing fractures [1]. A survey using online public open consultations with patients with XLH indicated that the disease burden becomes complicated and multifactorial with an increase in psychological issues [17].

Table 1. Clinical features and disease burden [6,16].

Bone, growth plate	Rickets * or osteomalacia, short stature
Cartilage	Early osteoarthritis
Kidney	Nephrocalcinosis, nephrolithiasis, chronic kidney disease, hypertension
Cardiovascular system	Hypertension, possible left ventricular hypertrophy
Ligament and tendons	Enthesopathy
Muscle	Muscle weakness, pain, stiffness
Skull	Craniosynostosis *, Arnold-Chiari type 1 malformations
Spine	Spinal stenosis
Teeth	Dental necrosis with severe abscesses, periodontitis, tooth loss
Ear	Hearing loss
QoL-related burden	Pain, physical deformities, dental complications, muscle weakness, stiffness, fatigue, mood alterations/depression, surgical procedures

*, specific to children.

Experts in metabolic bone diseases are commonly endocrinologists, nephrologists, and geneticists (pediatric and/or adult) who liaise with a patient's local health care providers (HCPs) (internist, general practitioner, pediatrician, and advanced practice providers), radiologists, orthopedic surgeons, physical therapists, rheumatologists, and dentists. As needed, the following professionals may be involved in patient care: neurosurgeons, otolaryngologists, ophthalmologists, audiologists, orthodontists, dieticians, rehabilitation specialists, pain management specialists, genetic counselors, occupational therapists, and social workers or psychologists [1]. Since XLH presents with a number of symptoms and signs in addition to the musculoskeletal system, the expert in metabolic bone diseases needs to be at the center of patient care and coordinate and collaborate with other professionals. Evidence for the disease burden of XLH during adulthood, as early as 20 years of age, is accumulating [2,18–24]. In addition, a new therapy targeting FGF23 has been developed and applied to clinical practice for children and adults [25–27]. The appropriate transition and effective transfer from pediatric HCPs to adult HCPs is essential for patients with XLH.

3. Transition

Increased survival from a wide range of chronic illnesses has resulted in greater numbers of children with disabilities reaching 20 years of age [28]. In 2002, a consensus

statement by the American Academy of Pediatrics (AAP), the American Academy of Family Physicians (AAFP), and the American College of Physicians (ACP)—American Society of Internal Medicine was published, and the statement mentioned the importance of facilitating the transition of adolescents with special health care needs into adulthood [29]. In 2011, the AAP, AAFP, and ACP with the authoring group published a clinical report entitled "Supporting the Health Care Transition (HCT) from Adolescence to Adulthood in the Medical Home" [30]. This report describes the process for transition preparation, planning, tracking, and completion for all youths and young adults (AYAs) beginning in early adolescence and provides a structure for training and continuing education to understand the essence of adolescent transition. In 2018, the clinical report was updated to provide more practice-based guidance on key elements of the transition; however, the policy and algorithm was not changed [31]. HCT is defined as "the process of moving from a child model to an adult model of health care with or without a transfer to a new clinician". The purpose of HCT is to decrease the numbers of patients that are lost to follow-ups and improve the quality of care through organized navigation that is provided to AYA patients and their caregivers. Patients that are lost to the follow-up do not receive appropriate practice management. Experts in XLH are commonly endocrinologists, nephrologists, and geneticists, although this depends on the countries and institutes that see patients with XLH. In general, geneticists are thought to see patients in both childhood and adulthood, rather than endocrinologists and nephrologists, who are usually either pediatric- or adult-specific. In some situations, a clinician that is familiar with pediatric and adult patients with XLH may continue to follow the patients through their life and provide them with proper medical care.

Transition barriers, including a fear of a new health care system and/or hospital, inadequate planning, and system difficulties, are experienced by AYAs and their families [31]. The greatest barrier mentioned is the difficulties that are associated with leaving their pediatric clinicians with whom they have had a long-standing relationship. Clinicians also find many transition barriers, such as communication and/or consultation gaps, training limitations, care delivery, care coordination, staff support gaps, a lack of patient knowledge and engagement, and a lack of comfort with adult care. The most common impediments are the lack of communication and coordination and the different practice behaviors between clinicians. Core elements in HCT consist of transition policy, transition tracking and monitoring, transition readiness, transition planning, transfer and/or integration into adult-centered care, and transition completion and ongoing care with adult clinicians. The process of HCT may be divided into three stages: (1) setting the stage: the initiation of HCT planning and a transition readiness assessment; (2) moving forward: the ongoing provision of HCT services; (3) reaching the goal: the transfer to adult healthcare services [32]. Based on expert opinions and limited research evidence, HCT planning needs to start at approximately 10 to 12 years of age for children with chronic conditions. Fruitful HCT requires collaborations between pediatric and adult-focused providers and settings that encourage AYA to continue to increase skills, even into their mid-20s. Effective HCT needs to be delivered in a similar culture and linguistic background based on the unique necessities of each AYA. An assessment of HCT readiness will direct interventions that lead to better outcomes and quality of life for AYAs.

4. Transition in Rare Diseases

Since HCT requires the efforts and contributions of pediatric and adult care providers, as well as the patient and parent, the benefits of HCT programs have been evaluated. Four randomized controlled trials, including cystic fibrosis, inflammatory bowel disease, type 1 diabetes, heart disease, and spina bifida, which aimed to improve the transition of care for adolescents from pediatric to adult health services, suggested positive effects on patients' knowledge of their condition, self-efficacy, and confidence [33]. A systematic review evaluating 43 studies on multiple chronic conditions demonstrated that HCT interventions often achieved positive outcomes, with the most common being adherence to care and the

use of ambulatory care in adult settings [34]. In contrast, despite the well-depicted transition position statement, patients with type 1 diabetes have experienced gaps in care during the transition period between pediatric and adult care. Five recommendations for the effective receivership of AYAs with type 1 diabetes have been established: communication between pediatric and adult HCPs; an objective assessment of patient knowledge; the patient and adult provider relationship; support for psychosocial needs for AYAs; and a team-based approach [35].

Difficulties are associated with the application of traditional health care models for common diseases to rare diseases, which have specific challenges. A survey revealed educational and knowledge gaps in HCPs that were related to rare endocrine conditions [36]. Medical self-management skills, including medical knowledge, practical skills, and communication in adolescents with rare endocrine conditions were recently reported to be insufficient [37]. The authors recommended three elements to improve transition readiness: the repeated provision of individualized medical information; the use of a transition checklist; and training communication ability with the help of parents, caregivers, and/or e-technology. HCT models have been reported for rare diseases, such as hemophilia [38], sickle cell disease [39], and phenylketonuria [40]. Key barriers to rare diseases include a lack of access to disease experts, limited knowledge on the disease course, and few patient–clinician research collaborations for the diseases [41]. A care continuum model for patients with rare diseases has been proposed that emphasizes the implementation of telehealth using modern e-technologies to reduce these barriers. A technology program using web and texting interventions in adolescents with chronic diseases was shown to improve the performance of disease management tasks, health-related self-efficacy, and patient-initiated communications [42]. The integration of telemedicine (an audiovisual interaction between a patient and HCP using computers, mobile devices, or telephones) may promote the care of AYAs with rare diseases, such as XLH, by improving access to disease experts, which may be limited due to physical distance and/or COVID-19-related restrictions, and supporting HCT [1]. Telemedicine appointments have been substituted for face-to-face visits with permission from the national health insurance system. Although telemedicine has allowed HCPs to deliver care to their patients during the COVID-19 pandemic, management challenges for endocrine conditions, including no physical examination and laboratory and radiographic evaluations, have been described [43].

Among rare bone disorders, HCT to adult-focused care for osteogenesis imperfecta (OI) has been reported. OI is a rare inherited disorder that is characterized by decreased bone mass and bone fragility and needs a multidisciplinary care team for patient management. Therefore, HCT for patients with OI is similar to that for XLH. The OI Foundation, the only voluntary US national health organization for OI, lists goals for the physician caring for a young adult with OI: "Maintain the current health status, preserve or improve the level of function, assure the continuity of medical and surgical care, and provide psychosocial support with referral to counseling and other services if needed" based on the relevant documents [44,45] (https://oif.org/wp-content/uploads/2019/08/Fact_Sheet_Transition_from_Pediatric_to_Adult_Care.pdf, accessed on 4 July 2022). They also show important transition topics for AYAs with OI, as follows: "Taking responsibility for one's own health care, being knowledgeable about OI in general and how it changes after puberty, knowing their personal health history, being able to communicate confidently with physicians, understanding how their health insurance works, and having identified adult care resources who are informed about OI. An interprofessional expert task force at Shriners Hospitals for Children in Canada reviewed the literature, developed guidelines for HCT for children with OI to adult healthcare services, and created a transfer summary tool [46]. The transfer tool includes "contact information, general information, psychosocial information, general medical information, family history, medical diagnosis and history, currently prescribed medications, recent laboratory results and x-rays, rehabilitation services, medical equipment, orthotics and assistive devices, functional capabilities and independence level, follow-up requirements, other professionals involved and community services, and general

concerns". The goals for the physician, the issues for the young person, and the transfer tool in OI provide important insights for establishing HCT for patients with XLH, because OI is a rare inherited musculoskeletal disorder with occasional non-musculoskeletal manifestations, such as XLH.

5. Transition in XLH

Regarding HCT for XLH, patient advocacy organizations for XLH, such as the XLH Network in the US and XLHuk in the UK, and for various rare diseases, such as the Genetic and Rare Diseases Information Center and National Organization for Rare Disorders in the US, provide patients with information on their disease. The international XLH alliance, consisting of more than 23 organizations worldwide, has been established to amplify the voices of patients with XLH and set a global multi-disciplinary standard of care and research. The XLH Network developed a toolkit on the transition from pediatric to adult care for patients and their caregivers (http://www.xlhnetwork.org/application/files/1916/0311/3210/XLH_TRANSITIONS_TOOLKIT.pdf, accessed on 4 July 2022), as well as the "Voice of the Patient Report", about the symptoms and treatment of XLH (http://www.xlhnetwork.org/application/files/5515/9317/2550/VOP_Report.pdf, accessed on 4 July 2022). Gianni et al. emphasized that the transition to adult care is a responsibility that is shared by the pediatric and adult teams involved in XLH, because XLH involves lifetime multi-organ morbidities that are associated with age [3]. Dahir et al. provided expert recommendations on HCT for patients with XLH [1]. Three areas of competency have been described: patient foundational knowledge, information transfer, and timelines and supportive behaviors to drive engagement. The timelines of transfer include transition readiness tracking, the initiation of assessments on transition readiness, transition planning, transfer of care, and post transfer (Table 2). Even though ages are mentioned in the timelines, HCT plans need to be individualized. Of note, age- and sex-specific patterns in growth velocity and bone mineral acquisition are distinct between girls and boys, especially in adolescence [47]. Girls reach both peak height velocity and peak bone-mass gain at a younger age than boys. The difference of the patterns in growth and bone accretion between females and males needs to be considered in HCT. It is important to begin the transition process in early adolescence and regularly assess transition readiness. The transition documents for patients with XLH include patient information, healthcare information, disease history, XLH complications, treatment history, the support of advocacy groups, and education, such as XLH symptoms emerging in adulthood [1].

Table 2. Simple timelines of transfer [1].

12 years: transition readiness tracking	- Pediatric practice approach to transitioning to adult care - Educate patients about self-advocacy, self-care, shared decision-making, and self-sufficiency - Educate parents about guidance on encouraging children to succeed in disease ownership
14 years: initiate assessments of transition readiness	- Assess understanding of symptoms, treatment goals, lab results, making appointments, available resources, and legal and insurance age-related changes - Educate patients about disease and management - Assess transition readiness yearly from the ages of 13 to 17 years
17 years: transition planning	- Discuss the optimal time of transition - Checklist of medical, laboratory, and imaging histories for adult providers - Discuss potential dosing changes (pediatric to adult) - Identify adult providers - Connect with advocacy groups

Table 2. *Cont.*

18–26 years: transfer of care	- Confirm the first adult provider appointment - Establish a process to orient adolescents/young adults into practice
3–6 months post-transfer	- Confirm the transfer of care - Continue collaborations between pediatric and adult providers

6. Conclusions

XLH is the most common form of inherited disorders that are characterized by renal phosphate wasting, but it is a rare multisystem disease that is often perceived as a childhood disease. However, recent studies demonstrated that XLH is a long-term and progressive disease throughout adulthood with a worsening disease burden. The lifelong multidisciplinary care of patients with XLH is necessary. Therefore, HCT plays a vital role in patient care and management for continuous adult care. Pediatric and adult HCPs both need to act in HCT to improve the outcomes of AYAs with XLH. HCT will prevent the loss of AYAs to follow-ups during the transition to adult care and will also improve healthcare conditions throughout life.

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