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ABSTRACT

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ESCEO-WHOCC1
CLINICAL MANIFESTATIONS OF XLH THROUGHOUT THE LIFECOURSE

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X-linked hypophosphataemic rickets is a rare genetic cause for osteomalacia in adults. It is due to inactivating mutations in the *PHEX* gene leading to excess FGF23 concentrations in the blood. The increase in FGF23 downregulates the sodium phosphate transporter in the kidney leading to reduced renal phosphate reabsorption and excessive urinary phosphate loss. There is also the downregulation in 1aOHase, leading to inappropriately low levels of 1,25-hydroxyvitamin D. Chronic hypophosphataemia is associated with skeletal and non-skeletal features.

The skeletal complications include the effects of long limb deformity that developed during childhood growth. This includes varus or valgus deformity, which reduces mobility, gait efficiency leading to increased fatigue, joint degeneration and pseudofractures. Pseudofractures can present with referred pain and should be excluded by imaging the bones below and above the region of pain. Another common but unexplained manifestation of XLH is a mineralising enthesopathy that affects the hip, spine and ankles and presents with limited joint movements. Joint movements can also be limited by joint capsule thickening and muscle stiffness. In the spine, the ossification of the ligamentum flavum and facet joint hypertrophy can lead to critical spinal cord compression with loss of sensation weakness and interference in bladder and bowel function. Joint pain can also be due to premature osteoarthritis or degenerative change, which causes weight-bearing pain, night pain, limited mobility and fatigue. This is exaggerated by limb malalignment deformity of the lower limbs. Further, osteomalacia can cause a deep bone ache that can be difficult to manage and often leaves patients labelled as having widespread chronic pain.

Neurological symptoms include spinal stenosis and an Arnold Chiari malformation. The symptoms of an Arnold Chiari malformation depend on the severity of the herniation of the cerebellum and brain stem into the cervical canal. A common symptom is suboccipital headaches and neck pain which is worse with the Valsalva manoeuvre. There can be visual and vestibular disturbance leading to dizziness, vertigo. The gait can become antalgic. There may be other cerebellar and lower cranial nerve signs causing tinnitus, vocal cord paralysis and sensitive or reduced hearing. More non-specific features include generalised fatigue and pain in the extremities or distal peripheral neuropathy. Patients can present to the respiratory team with evidence of sleep apnoea which can be obstructive from pharyngeal muscle weakness or central from brain stem respiratory centre compression. The dysphagia can lead to recurrent aspiration pneumonia and bronchiectasis as well as hoarseness. Other symptoms include involuntary naps, nocturia and morning headaches. The communist non-skeletal manifestation is recurrent dental abscesses which can lead to premature tooth loss. It is important that dental practitioners with expertise and experience in XLH are involved to ensure treatments are proportionate and effective. Dental radiographs may be needed to exclude osteomyelitis of the jaw in patients with severe infections. Manifestations of XLH may be due to complications from phosphate and activated vitamin D therapy, including secondary and tertiary hyperthyroidism, renal stones and nephrocalcinosis. Finally, the chronic pain and reduced mobility can often lead to significant issues with mental health with increased risk of depression and anxiety. Understanding the range of clinical features is critical to ensuring patients receive optimal management, including early recognition of potentially life-changing and life-shortening complications.

ESCEO-WHOCC2

THERAPEUTIC APPROACHES OF XLH THROUGHOUT THE LIFE COURSE

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X-linked hypophosphatemia (XLH), due to PHEX mutations, is the most frequent form of hypophosphatemic rickets/osteomalacia. XLH is a dominant disorder with a prevalence of approximately 1.7/100,000 children to 4.8/100,000 persons. XLH represents approximately 80% of all cases of XLH up to 87% of familial cases and 72% of sporadic cases. XLH is X-linked dominantly inherited; hence, there are twice more affected girls than boys. *PHEX*, the gene responsible for XLH, was identified on chromosome Xp22. It codes for a cell surface-bound protein-cleaving enzyme expressed predominantly in the bone and teeth. The altered function of this bone-derived endopeptidase causes both the mineralization defect and the renal phenotypic abnormalities of XLH. The molecular defect in PHEX leads to an increase production of circulating FGF23. FGF23 is critical in controlling serum phosphate level through the reabsorption of phosphate in the renal proximal tubule. In situations where FGF23 is produced in excess, phosphate leaks through the kidney in the urine; hence, serum phosphate is below the normal range. In addition, FGF23 has a strong inhibitory effect on 1,25(OH)2D synthesis, hence reducing calcium absorption through the gut. Therefore, patients with PHEX mutation usually present with low serum phosphate, mildly decreased serum calcium, phosphate wasting, and reduced 1,25(OH)2D levels. The abnormal phosphate level, the defect in 1,25(OH)2D synthesis, and the accumulation of ASARM peptides lead to an impaired mineralization of the skeleton and ultimately, rickets, osteomalacia, and insufficient growth.

The clinical manifestations of XLH occur most often around the age of walking, despite an adequate vitamin D supplementation. In children, the primary clinical symptoms are skeletal pain and deformity, abnormal gait, decreased growth velocity, dental abscesses, and craniosynostosis. In the absence of diagnosis and/or treatment, short stature worsens progressively until the age of 5 years and becomes disproportionate. This may lead to extreme short stature with an adult height below − 2 SD. Tooth eruption is often delayed, but, when present, teeth display a normal enamel. The impaired mineralization of dentin is the cause of dental abscesses and early decay of lacteal and permanent teeth. Young adults present with increased frequency of periodontitis and altered perialveolar bone. In adults, osteomalacia, bone pain, stiffness, and enthesopathy (calcification of tendons, ligaments, and joint capsules) are typical findings. Hypertension, left ventricular hypertrophy, and cardiac insufficiency have been sporadically described in children and young adults. Dizziness and deafness due to abnormalities of the inner ear may develop towards adulthood. Many patients may have partial synostosis of the sagittal sutures leading to a dolichocephalic shape of the head. This may be accompanied by intracranial hypertension. Type 1 Chiari malformation is a complication of XLH in about 25% of the patients, triggering the search for headaches and neck pain. XLH is characterized by elevated ALP, low serum phosphate, phosphate wasting, and elevated levels of circulating FGF23.

The diagnosis of XLH is based on clinical, radiological, and biochemical findings. The X-linked inheritance strongly argues for the diagnosis. FGF23 is not available everywhere and is not fully mandatory for the diagnosis. In a subset of patients without familial history, i.e., one third of the patients, mutational analysis of *PHEX* is recommended. In case of atypical features and/or lack of *PHEX* mutation, further work-up is recommended.

In children, the conventional treatment of XLH associates vitamin D analogues and repeated doses of phosphate supplements. Active vitamin D analogues are given to counter calcitriol deficiency, prevent secondary hyperparathyroidism, and increase phosphate absorption from the gut without normalizing phosphate levels. The objectives of treatment are to heal rickets, improve growth, and near normalize ALP. The continuation of conventional treatment in adults is debated yet may help to prevent the dental disease. The human anti-FGF23 monoclonal antibody, burosumab, is now an alternative to the conventional therapy as it was approved by the Food Drug Administration (FDA) for adults and children above 1 year of age and by the European Medicines Agency (EMA) in children and is now available in some countries. Administered subcutaneously to XLH children twice a month, burosumab demonstrated favorable clinical and biochemical effects, i.e., radiographic improvement of rickets, improved distance during the 6-min walk test, increase in serum phosphate, increase in TmP/GFR, and increase in $1,25(OH)_2D$. Patients with severe rickets show greater rickets, growth, and biochemical improvement under burosumab than upon conventional therapy. Most side effects are reactions at the site of injection. Burosumab is therefore an alternative in children refractory or do not respond adequately to the conventional therapy or in patients with severe rickets. In adults, burosumab treatment induces an improvement in serum phosphate and biochemical markers such as Tmp/GFR and 1,25(OH)2D and more importantly in quality of life scales, e.g., WOMAC, and SF36, and in skeletal outcomes such as fracture healing and pain. Adjuvant therapies are sometimes required. The administration of growth hormone (rhGH) improves growth in prepubertal children with XLH, but no clear indication exists

to support systematic treatment of patients with XLH. Surgery is indicated for severe bowing or tibial torsion unlikely to improve with medical management alone. Except in extremely deformed limbs, corrective osteotomies (a surgical procedure in which a bone is cut to straighten it) are usually not performed in children before puberty, as medical therapy improves bow deformities until this age. Eight plates guided growth surgery have been used in young children yet seems to give better results in *valgus* deformities and have not been evaluated until the end of growth. Finally, the multidisciplinary management of these patients is mandatory; adolescence, pregnancy, and menopause are critical for patients and may imbalance the disease.