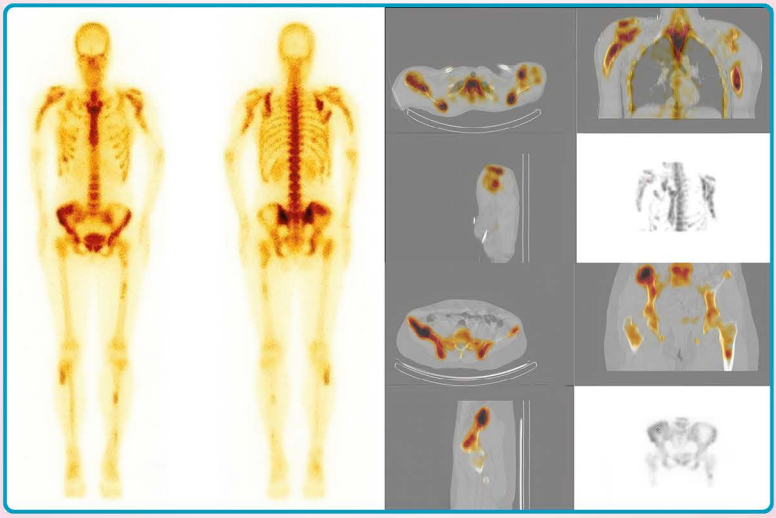
Pohybové ústrojí

Pokroky ve výzkumu, diagnostice a terapii



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OBSAH

KASUISTIKY

ZPRÁVY

NEUROFIBROMATÓZA TYPU 1: KOMPLEXNÍ MULTISYSTÉMOVÉ ONEMOCNĚNÍ Z POHLEDU KLINICKÉHO GENETIKA

NEUROFIBROMATOSIS TYPE 1: A COMPLEX MULTI-SYSTEM DISORDER FROM THE PERSPECTIVE OF A CLINICAL GENETICIST

Krulišová Veronika[1], Michalovská Renáta[1], Vlčková Zděnka[1], Ivo Mařík[2,3]

[1] GHC Genetics; Prague, Czech Republic

[2] Centre for Defects of Locomotor Apparatus I.l.c.; Prague, Czech Republic

[3] Faculty of Health Care Studies, West Bohemia University; Pilsen, Czech Republic

SUMMARY

Neurofibromatosis refers to several related genetic disorders that have overlapping clinical manifestations. The aim of this article is to introduce Neurofibromatosis type 1 (NF1, OMIM #162200), a common autosomal dominant genetic disorder from the perspective of clinical geneticist.

Management of NF1 is multidisciplinary and aimed at addressing the diverse range of clinical manifestations and complications associated with the disorder.

Genetic counseling is an integral component of NF1 management providing affected individuals and their families with information about the inheritance pattern, recurrence risk, and available testing options.

Key words: Neurofibromatosis type 1, genetic counseling, *NF1* gene, causal variant, next-generation sequencing, Sanger sequencing

INTRODUCTION

Neurofibromatosis type 1 (NF1, i.e. Neurofibromatosis von Recklinghausen) is a multi-system disorder characterized by involvement of the skin, central and peripheral nervous system, changes in the iris of the eye, bone changes and an increased risk of developing malignant tumors.

ORIGINAL DIAGNOSTIC CRITERIA (1988)	UPDATED DIAGNOSTIC CRITERIA (2021)
A diagnosis of NF1 can be given if an individual has two or more of the following manifestations: • Six or more café-au-lait macules (brown skin spots) » greater than 5mm in pre-pubertal children » greater than 15mm in post-pubertal individuals • Freckling in axilla (armpit) or groin • Two or more neurofibroma tumors of any type, or one plexiform neurofibroma • Two or more iris Lisch nodules (iris hamartomas) • Optic glioma • A distinctive bony lesion: dysplasia (abnormal growth) of the sphenoid bone behind the eye, or dysplasia of long bones, often in the lower leg • Having a close relative (parent, sibling, or child) with NF1	A diagnosis of NF1 can be given if an individual has two or more of the following manifestations: • Six or more café-au-lait-macules* (brown skin spots) » greater than 5mm in pre-pubertal children » greater than 15mm in post-pubertal individuals • Freckling in axilla (armpit) or groin* • Two or more neurofibroma tumors of any type, or one plexiform neurofibroma • Two or more Lisch nodules or two or more choroidal abnormalities • Optic pathway glioma (tumor of the visual pathway) • A distinctive osseous lesion such as: sphenoid dysplasia; anterolateral bowing of tibia (tibial dysplasia); or pseudarthrosis of a long bone • A pathogenic NF1 gene variant ** • A parent with NF1 by the above criteria *At least one of the two pigmentary findings (café-au-lait macules or freckling) should be bilateral.

Fig. 1: Legius E.et al. Revised diagnostic criteria for neurofibromatosis type 1 and Legius syndrome: an international consensus recommendation. Genet Med. 2021 Aug;23(8):1506-1513. doi: 10.1038/s41436-021-01170-5. Epub 2021 May 19.

NF1 is primarily characterized by the development of neurofibromas, benign tumors originating from peripheral nerves, and café-au-lait spots, a hyperpigmented skin lesions.

Individuals with NF1 may develop other characteristic features, such as Lisch nodules (hamartomas of the iris), axillary or inguinal freckling, skeletal abnormalities, optic pathway gliomas, and cognitive deficits.

The disease is fully penetrant. Symptoms manifest from childhood to adulthood and have a progressive character. The severity and progression of NF1-associated complications can vary widely among affected individuals, ranging from mild to severe, even within one family.

According to epidemiological research, the rate of cancer occurrence in individuals with NF1 is roughly four times greater than that of the general population (**6**). Approximately 10% of NF1 patients develop malignant peripheral nerve sheath tumors, typically originating from plexiform neurofibromas. Additionally, NF1 is commonly linked with pheochromocytoma, sarcoma, melanoma, breast cancer, ovarian cancer, leukemia, and gastrointestinal stromal tumors.

NF1 incidence is between 1:2,500 and 1:4,000 and is one of the most common rare diseases. Approximately 50% of *NF1* gene causal variants arise *de-novo* (**2**) and 50% of NF1 cases are hereditary and transmitted in autosomal dominant manner.

Formal diagnostic criteria for NF1 have been established. Diagnosis is primarily based on revised clinical criteria established by the National Institutes of Health Consensus Development Conference in 2021 ((**3**), **Fig. 1**).

Since NF1 is a complex multi-system disease, differential diagnosis may be wide reflecting the most affected organ body system. Clinical geneticists typically consult patients with cutaneous manifestation where for example diagnosis as Legius syndrome, Noonan syndrome, McCune-Albright syndrom should be considered in the differential diagnosis.

NF1 gene

NF1 is caused by germline pathogenic variants (nonsense, frameshift, missense, splicing mutations, small in frame deletions a duplications) in the *NF1* gene located on chromosome 17q11.2 and rarely by 17q11 microdeletion (approx. 5–7%; (**8**)). The *NF1* gene spans approximately 350 kilobases and contains 60 exons (57 constitutive exons, plus 3 alternative spliced exons), making it one of the largest genes in the human genome.

According to Online Mendelian Inheritance in Man database (OMIM; i.e. catalog of human genes and genetic disorders), *NF1* gene variants might be associated not only with NF1 (OMIM #162200) but also with related syndromes/subtypes such as Neurofibromatosis-Noonan syndrome (OMIM #601321), Neurofibromatosis, familial spinal (OMIM #162210) and Watson syndrome (OMIM #193520).

Besides generalized NF1 mosaic NF1 (MNF1) exists. MNF1 (also segmental NF1) is caused by postzygotic pathogenic variants in NF1. Manifestations of MNF1 are limited to the affected area of the body. Symptoms are usually unilateral but may appear bilaterally, either in a symmetric or asymmetrical form (**7**).

More than 3,000 causal *NF1* variants have been identified in NF1 patients (**5**). Described variants are distributed all over the whole gene. In general, there is no clear correlation between the clinical phenotype and molecular genotype in most *NF1* variants. However, few correlation studies exist with these particular examples:

NF1 whole-gene deletion causes severe form of the disease, characterized by cutaneous neurofibromas earlier in life, development of larger number of tumours, including malignant peripheral nerve sheath tumors, more frequent severe cognitive abnormalities, somatic overgrowth, and dysmorphic facial features (**4**).

3-bp deletion in *NF1* exon 17 (c.2970_2972delAAT) has been associated with typical pigmentary features of NF1 without cutaneous or surface plexiform neurofibromas (**9**).

Some evidence has suggested that the specific genotype may be the main determinant of the development of Optic Pathway Glioma (**10**).

NF1 protein

The *NF1* gene encodes a protein called neurofibromin, which is expressed in cells of the central and peripheral nervous system, leukocytes and, in low concentrations, also, for example, in fibroblasts and osteoblasts. Neurofibromin acts as a negative regulator of the RAS signaling pathway. This pathway plays a crucial role in controlling cell proliferation, differentiation, and survival. Neurofibromin functions as a GTPase-activating protein (GAP), which promotes the hydrolysis of RAS-GTP to RAS-GDP, thereby inactivating RAS. By inhibiting RAS signaling, neurofibromin helps regulate cell growth and prevent the formation of tumors.

Mutations in the *NF1* gene disrupt the normal function of neurofibromin, leading to dysregulated RAS signaling and abnormal cell proliferation. Loss of neurofibromin's GAP activity results in the accumulation of active RAS-GTP, which drives uncontrolled cell growth and tumor formation characteristic of NF1.

Genetic testing

Molecular analysis of *NF1* gene is challenging with regards to the large size of the gene, the lack of mutational hotspots and the existence of pseudogenes.

Next-generation sequencing (NGS), the multigene panel testing, allows accurate and fast detection of germline *NF1* variants. NGS approach shows higher sensitivity for detecting mosaic forms of NF1 compared to classic Sanger sequencing. Furthermore, multigene panel testing enables simultaneous analysis of many genes and thus differentiate NF1 from other syndromes that should be considered in the differential diagnosis.

Once the *NF1* causal variant is detected by the NGS approach, confirmation using classic Sanger DNA sequencing analysis performed on the corresponding exon follows. Large deletions and duplications of *NF1* are performed by multiplex ligation-dependent probe amplification (MLPA) analysis.

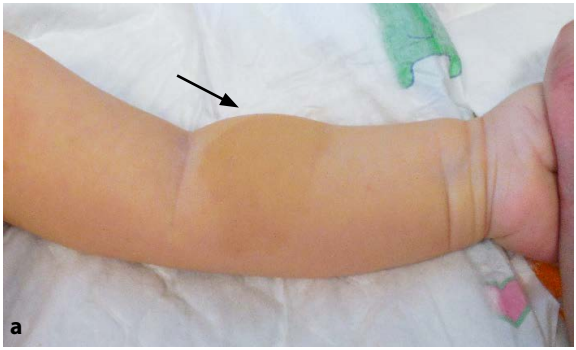
CAVE: In practice, we encounter patients in whom the causal *NF1* variant has not been detected. However, the absence of *NF1* pathogenic variant does not exclude the diagnosis. Molecular genetic methods also have their limitations leading to failure to identify the causal variant. For example, variants in regulatory regions and deep intronic variants represent the problematic molecular mechanism. Furthermore, other genetic symptoms and external factors must be taken into the account.

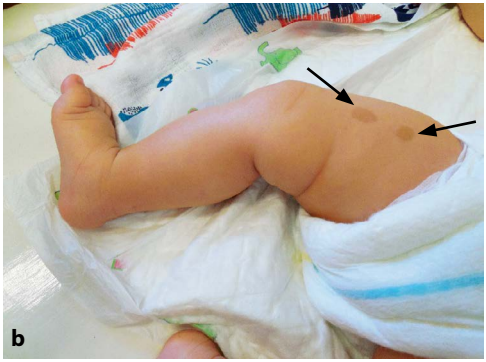
Genetic counseling

Genetic counseling is an integral component of NF1 management, providing affected individuals and their families with information about the inheritance pattern, recurrence risk, and available testing options.

Diagnosis of NF1 is primarily based on clinical criteria. However, genetic testing is recommended to confirm the diagnosis on molecular basis. The DNA analysis is particularly useful in cases where clinical features are inconclusive or atypical.

Beside patients with typical NF1 features, clinical geneticists consult often children with café-au-lait spots (**Fig. 2a, 2b, 2c**) and no other NF1 symptoms. According to literature 50% of children with sporadic NF1 younger than 2 years meet only a single criterion (**1**), usually café-au-lait spots. Therefore, *NF1* gene testing may lead to early recognition of NF1 in children following appropriate surveillance.





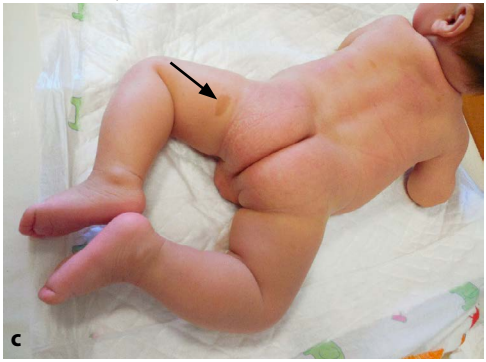


Fig. 2a, 2b, 2c:
Boy, 5 months old, cafe-au-lait spots

If the causal *NF1* variant has been identified in the child patient, genetic counseling and targeted testing should be offered to proband's relatives, who desire it:

1) If one of the proband's parent is affected with NF1, targeted DNA analysis of causal variant in *NF1* gene should be performed to confirm the diagnosis on molecular basis. As the inheritance is autosomal dominant, the risk that positively tested person will transmit the causal variant to offsprings is 50%.
2) Even if both parents are without NF1 symptoms, targeted testing of causal variant in both parents is recommended since mild and/or atypical forms are possible. If the unaffected parents are tested negative, we assume *de novo* occurrence of the mutation in the proband. However, germline mosaicism in one of the parent cannot be excluded, thus the recurrence risk of NF1 for proband's siblings has been up to 1%.
3) If one of the proband's parent is patient with segmental NF1 risk to offsprings is not predictable varying from 1 to 50%, depending on the degree of gonadal involvement.

Once the causal *NF1* variant has been identified, Preimplantation Genetic Testing for Monogenic disease (i.e. PGT-M) and prenatal testing may be offered to individuals with NF1 who are considering starting a family, allowing for informed reproductive decision-making and family planning.

CONCLUSION

Management of NF1 is multidisciplinary and aimed at addressing the diverse range of clinical manifestations and complications associated with the disorder. Treatment modalities may include surveillance for tumor growth and complications, surgical resection of symptomatic neurofibromas, medical management of associated conditions and supportive care to address cognitive and developmental challenges. Chemotherapy with selumetinib (Koselugo) is considered for patients with inoperable plexiform neurofibromas. It is believed that the NF1 diagnosis should include molecular testing since it leads to early recognition of NF1 in children and allows for appropriate surveillance.

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Author Address:
Veronika Krulišová, MD, PhD
GHC Genetics, Prague, Czech Republic
E-mail: krulisova@ghcgenetics.cz

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Adresa korespondenčního autora:

Ing. Karel Tesař, Ph.D.
FJFI ČVUT v Praze
Trojanova 13
120 00 Praha 2
e-mail: Karel.Tesar@fjfi.cvut.cz

COMPREHENSIVE TREATMENT OF HYPOPHOSPHATEMIC RICKETS. BRIEF OVERVIEW AND CASE REPORT

KOMPLEXNÍ LÉČBA HYPOFOSFATEMICKÉ KŘIVICE. KAZUISTIKA

Mařík Ivo[1,2], Myslivec Radek[2,3], Krulišová Veronika[4], Maříková Alena[2], Hudáková Olga[2], Vážná Anna[5], Zemková Daniela[6]

1 Faculty of Health Care Studies, West Bohemia University; Pilsen, Czech Republic

2 Centre for Defects of Locomotor Apparatus l.l.c.; Prague, Czech Republic

3 Orthopaedic and Traumatology Department of Hospital Pribram,; Příbram, Czech Republic

4 GHC Genetics; Prague, Czech Republic

5 Department of Anthropology and Human Genetics, Faculty of Science, Charles University, Prague, Czech Republic

6 Dept. of Paediatrics, Charles University, University Hospital Motol; Prague, Czech Republic

e-mail: ambul_centrum@volny.cz

SUMMARY

In this case report, we demonstrate a 26.5-year-old female patient with hypophosphatemic rickets. The diagnosis was made at 2 years of age. Conventional medical treatment was instituted from 2 years and 9 months. (Rocaltrol and Neutra phos and phosphate solution, respectively). The varus deformities of the tibiae were partially corrected with flexion-preloaded orthoses, which were used intermittently at night from 20 months to 7 years of age.

At 8 years of age, anterolateral curvature and varus deformity in the distal third of both tibias were addressed by two-level tibial osteotomy and intramedullary fixation according to Küntscher. Remodeling of the ostetomies of both tibias was demonstrated by X-ray examination 5 months after surgery. The planned operation for residual varosity of the left tibia at the end of the growth period was not performed due to the disagreement of one of the parents.

The current aim of the communication is to verify the transient compensation of calcium-phosphate metabolism by the effect of 6 months of administration of the drug burosumab (Crysvita) and to document the favourable healing of the corrective osteotomy of the tibia, which was performed at the age of 25 years at the patient's request (after the approval of the extraordinary reimbursement of the treatment with burosumab according to §16 of Act No. 48/1997 Coll., on public health insurance).

Burosumab reduces FGF23 activity, thereby reducing the loss of phosphate into the urine. A secondary consequence is compensation of calciophosphate metabolism and in this case positive effect on bone mineralisation and bone healing of osteotomy, which is significantly impaired and prolonged in adulthood with a risk of pseudoarthrosis.

Keywords: hypophosphatemic rickets, X-linked hypophosphatemia (XLH), lower limb deformities, conventional therapy, orthotic and surgical treatment, human monoclonal antibody IgG1/ Burosumab-twza, bone metabolism, bone healing in children and adults.

INTRODUCTION

Hereditary hypophosphatemic rickets is caused by mutations in various genes involved in the regulation of renal phosphate reabsorption (PHEX, FGF23, DMP1, ENPP1, CLCN5,) (**Rafaelen et al. 2013, Spranger et al. 2018, Unger et al. 2023**). The most common is the X chromosome-linked form, hypophosphatemic rickets (XLH).

This is a rare, severe genetic disease caused by inactivating mutations on the *PHEX* gene (phosphate-regulating gene with homologies to endopeptidases on the X chromosome) (**Chesher et al. 2018**). It is classified in group 27 called Disorders of bone mineralization according to GENETIC BONE DISORDERS NOSOLOGY: 2023 REVIEW (**Unger et al. 2023**).

The **incidence** of XLH (MIM No. 307800) is 3.9 per 100,000 live births. The **prevalence** ranges from 1.7 per 100,000 children to 4.8 per 100,000 persons (children and adults) (**Beck-Nielsen et al. 2009**).

XLH inheritance is *X-linked dominant*. However, approximately 20–30% of XLH cases are due to spontaneous mutations (**Rasmussen and Tenenhouse 1995, Marik et al. 2022**)**.**

Pathogenesis and **clinical manifestations**. XLH is characterized by hyperphosphaturia, hypophosphatemia, and defective bone mineralization (**Burnett et al. 1964; Imel et al. 2005; Spranger et al. 2018**). The underlying cause of hypophosphatemic rickets (XLH) is elevated fibroblast growth factor 23 (FGF23), which causes increased urinary excretion of phosphate and decreased production of 1,25-dihydroxyvitamin D /1,25(OH)2 D (**Imel et al. 2005, Beck-Nielsen et al. 2019**). Due to hypophosphatemia, bone mineralization is impaired (**Tiosano and Hochberg 2009**).

In children, **rickets** and **osteomalacia** develop. Both rickets and osteomalacia lead to impaired growth, deformities mainly of the lower limbs and spine and impaired mobility of the affected individual. There is an increased incidence of cranial synostosis and Chiari I malformation (**Rothenbuhler et al. 2019**). *In adulthood*, XLH manifests as **osteomalacia** due to chronic hypophosphatemia. Patients suffer from bone and joint pain as well as frequent so-called *reconstructive fractures (fatigue fractures, pseudofracture* (**Shore et al. 2013, Marik et al. 2022**). Joint pain is often polyarticular, mainly affecting hips, knees and ankles, often with signs of osteoarthritis (**Reid et al. 1989; Beck-Nielsen et al. 2010**). Adult patients also have a range of complications including non-traumatic

fractures, joint flexion stiffness, tendon mineralisation, osteoarthritis and recurrent dental abscesses (**Beck-Nielsen et al. 2010; Carpenter et al. 2011; Chesher et al. 2018; Spranger et al. 2018**).

In addition, many patients suffer from muscle dysfunctions due to impaired muscle phosphate metabolism and also muscle imbalances due to impaired lower limb mechanical axis (**Reid et al. 1989, Carpenter et al. 2011, Veilleux et al. 2012**). In men, skeletal impairment is more severe (**Hardy et al. 1989**). The severity of impaired calciophosphate metabolism tends to be variable, even within a single family. It is manifested by reduced capacity - functionality of the musculoskeletal system. Patients are affected by reduced mobility and fatigue with significant impact on activities of daily living, have difficulty completing education and have problems with employment (**Beck-Nielsen et al. 2010, Che et al. 2016**).

CONVENTIONAL TREATMENT

Conventional treatment consists of a combination of oral phosphate and vitamin D analogues. A review article on the diagnosis and treatment of XLH published by Carpenter et al. (**2011**) cites several peer-reviewed publications on the conventional treatment of paediatric patients with XLH (**Glorieux et al. 1980**; **Harrell et al. 1985**; **Verge et al. 1991**; **Costa et al. 1981**; **Rasmussen et al. 1981**). These are mainly individual and pooled case studies and retrospective studies. The current status of diagnosis and treatment is reviewed by Cardenas-Aguilera et al. **(2024).**

However, an exact evaluation of the benefits and risks of this treatment has only recently begun to emerge, compared with new more effective therapies (**Dodamani et al 2024**). Conventional treatment has already led to a reduction in radiological signs of rickets (Thacher's total rickets severity score) and deformities (RGI-C scale), but the efficacy was not sufficient. Chesher et al. (**2018**) followed 59 adult patients (17–79 years) who were treated with conventional therapy. Twenty-seven of these patients (45.8%) had undergone osteotomy or corrected growth using a staple fixation system in their lifetime (**Horn et al. 2017**, **Novais and Stevens 2006**), two patients had bilateral knee replacements, and two patients had hip replacements. Dental abscesses occurred in 24 patients (41%), and the other most common problems included dental caries and missing teeth.

It is very well known that conventional treatment does not adjust the small stature of patients. Even in patients who respond to standard treatment, severe growth failure occurs in 25–40% of cases, leaving patients with a final height below -2 SD (**Linglart et al. 2014**; **Zemkova et al. 2021**).

In addition to the lack of efficacy of conventional treatment, adverse events (gastrointestinal symptoms such as: diarrhea, abdominal pain) and risks should also be pointed out. Among the most serious are **nephrocalcinosis** and **hyperparathyroidism (Scheinman et al. 2018**). Nephrocalcinosis develops in up to 80% of XLH patients treated with conventional therapy. Its severity correlates closely with the dose of phosphate (**Carpenter et al. 2011**; **Taylor et al. 1995**). Another side effect of conventional therapy is **secondary** (SHP) or **tertiary** (THP) **hyperparathyroidism** (**Scheinman et al. 2018**; **Tournis et al. 2011**).

The controversial topic is therefore conventional treatment in adulthood after growth has ceased. Various authors agree that conventional treatment is indicated in the presence of symptoms. Routine administration of treatment in asymptomatic adults is not recommended (**Haffner et al. 2019**, **Linglart et al. 2014**; **Cárdenas-Aguilera et al. 2024**). Re-initiation of treatment is considered in the presence of active osteomalacia or associated conditions, and during pregnancy and lactation.

In 2018, the U.S. Food and Drug Administration (FDA) approved Crysvita (burosumab-twza, a human IgG1 monoclonal antibody against FGF23) for the treatment of adults and children aged 1 year and older with X chromosome-linked hypophosphatemia (XLH). Later, burosumab was approved by The European Medicines Agency (EMA) for the treatment of XLH rickets for European Union countries.

New drug Crysvita (burosumab) is available in the Czech Republic from 2019. It is a recombinant human monoclonal antibody (IgG1) that binds to fibroblast growth factor 23 (FGF23) and inhibits its activity. Burosumab increases tubular reabsorption of phosphate in the kidney by inhibiting FGF23, thereby increasing serum 1,25-dihydroxy-vitamin D concentrations. It is indicated for the treatment of X-Linked Hypophosphataemia (XLH) with radiographically proven bone disease in children aged 1 year and older and in adolescents with growing skeletons. The recommended initial dose is 0.8 mg of burosumab per kg body weight given every two weeks. The maximum dose is 90 mg (Crysvita SPC).

In the last agreement with the General Health Insurance Fund of the Czech Republic it was determined that burosumab can be used: 1. in case of severe intolerance to conventional therapy; 2. if conventional therapy for more than one year is not effective (no improvement in growth deficit; Rickets Severity Score decreases by less than 0.5).

Treatment with burosumab in pediatric patients with XLH aged 5–12 years significantly improved tubular phosphate reabsorption and serum phosphorus levels, which corresponded with a reduction in rickets severity. The healing of rickets also likely contributed to improved growth and physical activity in patients (**Carpenter et al. 2018**). The difference from conventional treatment is significant (**Dodamani et al. 2024**; **Imel et al. 2017, 2021**; **Olivotto et al. 2024**). Adverse events have not yet been observed. First experiences from the Czech Republic have been published in case reports (e.g. **Flögelová 2021**; **Maratová and Šumník 2021**). In newly diagnosed patients, burosumab is recommended as first choice treatment before phosphate and vitamin D (**Scheinman et al. 2018**). However, for economic reasons, conventional treatment is usually started and burosumab is switched to in children if it is insufficiently effective or poorly tolerated (**Cárdenas-Aguilera et al. 2024**).

Burosumab is also the treatment of choice **for adults** with XLH in the treatment of fractures, corrective osteotomies, stress fractures and hyperostosis and other bone damage due to metabolic bone disease (**Scheinman et al. 2018**). Lafage-Proust (**2022**) presents a comparison of burosumab and convalescent therapy in adults based on a randomised 24-week placebo-controlled trial followed by an equally long study with burosumab (dose 1 mg/kg/4 weeks) in 134 adults with XLH. During treatment with burosumab, 94% of patients experienced normalisation of serum phosphate compared with 7% in the placebo group. Fracture healing increased 16.7-fold compared to placebo-treated patients. All pain and disability tests improved in a time-dependent manner. Burosumab at 48 weeks improved histological lesions of osteomalacia in a single-arm longitudinal study analyzing

paired bone biopsies. No hyperphosphatemic episodes were detected. Overall, the benefit-risk ratio of burosumab in adult patients with clinical and/or biological complications of XLH is positive. Treatment with burosumab will undoubtedly also prevent the adverse effects of conventional vitamin D3 and phosphate therapy, namely nephrocalcinosis and hyperparathyroidism (**Haffner et al. 2019**; **Portale et al. 2019**; **Lafage-Proust 2022**; **Brandi et al. 2022**; **Marik et al. 2022**), as recent work has already shown (**Olivotto et al. 2024**; **Dodomani et al. 2024**).

The aim of our case report was to present the results of conventional and orthopaedic treatment in a patient with XLH and to verify the transient compensation of calcium phosphate metabolism (normalization of hypophosphatemia) by the effect of 6 months of burosumab (Crysvita) administration and to document the favorable healing of a corrective osteotomy of the left tibia, which was performed in adulthood at the patient's request.

CASE REPORT

History

The patient was born to unrelated parents (23 and 37 years old). *Family history* was not significant from genetic point of view. The child is from the mother's 2nd pregnancy (the first pregnancy ended as a miscarriage). Delivery due to maternal hypertension was induced 2 days after term, breech position, not crossed, b.w. 3200 g, b.l. 50 cm, icterus not detected. From 2 weeks of age she was taking vitamin D (Vigantol gtt.). Prevention of hip development was normal. Psychomotor development was not delayed. She walked independently at 10 months. At 13 months, due to suspicion of rickets (wide wrists, ankles, rachitic rosary, crura vara bil.) she was hospitalized at the Children's Clinic in Brno with the conclusion of **rickets** (X-ray of the left hand – cup-shaped enlargement of the distal metaphysis of the radius and ulna, low serum phosphorus level and high value of total alkaline phosphatase /ALP/). Parenteral administration of Calciferol injection (300 000 I.M.) had no effect on the values of biochemical markers in blood serum (phosphorus and ALP).

At the age of 2 years, the diagnosis of **hypophosphatemic rickets** was made, which was subsequently confirmed at the age of 25 years by molecular genetic testing. DNA analysis revealed missense pathogenic variant c.1601C>T (p.Pro534Leu) in the *PHEX* gene in a heterozygous state. This variant has already been detected in patients with XLH. It has also been observed to segregate with disease in related individuals. Since both parents of our patient do not show symptoms typical for XLH, we presume *de novo* occurance in the patient. Conventional treatment was started at 2 years and 9 months (Rocaltrol cps. 0.25 ug /3x1/ and Neutra Phos /1 sachet divided into three doses/, later replaced by phosphate solution 3 ml 5 times a day). Conventional treatment and biochemical monitoring was conducted in cooperation with Prof. MUDr. J. Zeman, DSc. (Department of Child and Adolescent Medicine, 1st Medical Faculty, Charles University in Prague). Despite the above mentioned therapy, serum phosphorus values were repeatedly low and total alkaline phosphatase high, calcemia and calciuria were normal. Between 2007 and 2011, i.e. from 9 to 13 years, conventional treatment was discontinued due to family non-cooperation.

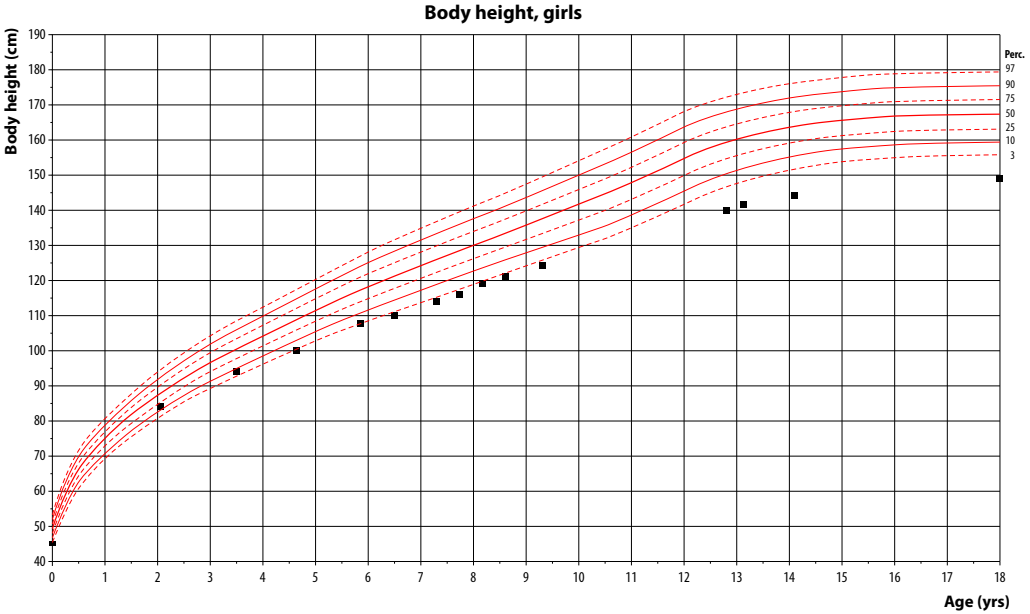

Fig. 1a. growth chart of our proband in comparison with Czech standards (2001) (**Zemková a Mařík 2021**).

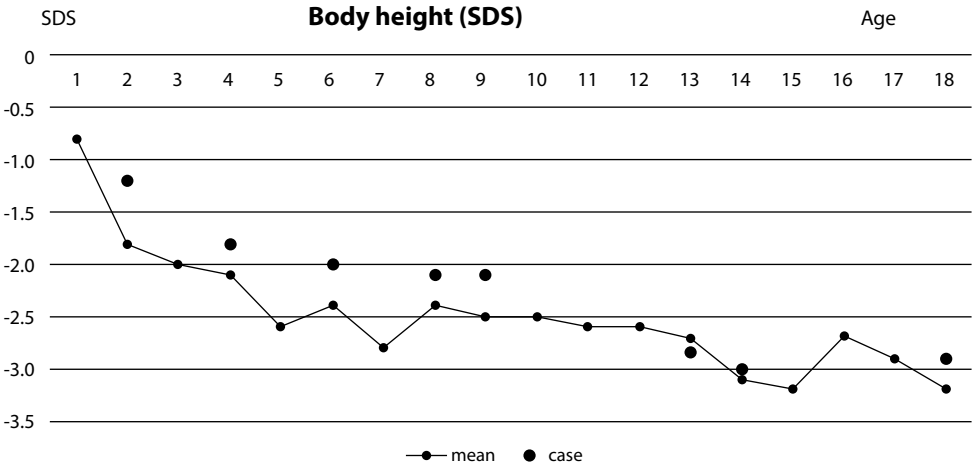

Fig. 1b. body height (SDS) – comparison with mean growth curve of our group of XLH children (**Zemková a Mařík 2021**).

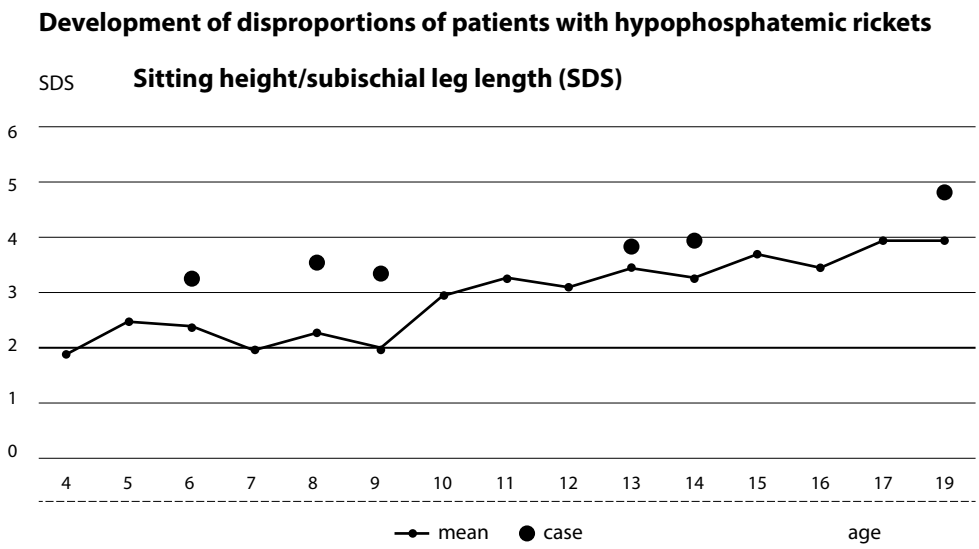

Fig. 1c. development of relation of sitting height to subischial leg length (SDS); comparison with our group of XLH children) (**Zemková a Mařík 2021**).

Phenotype of the patient – see **Fig. 1–6**.

The growth parameters and proportionality during growth were consistent with the diagnosis – **Fig. 1a–c**: mild short stature (-2.1 SD) – **a, b**; Shortening of the lower extremities was within the variability limits of Czech patients with hypophosphatemic rickets – **c**. Discontinuation of treatment resulted in growth retardation compared to the mean value of Czech patients (**Zemková a Mařík 2021**) – see **b**.

The **orthopaedic treatment** took place at the Centre for Defects of Locomotor Appartus in Prague. From the age of **2 years**, she was treated for varosity of the tibiae with preloaded orthoses (intermittent application for 10 h overnight) with good correction of varosity in the knees – see **Figs. 2a–e**, **3a–d**. However, with growth, progression the tibial varosity in the supramalleolar region was observed with radiographically detected overgrowth of the distal ends of the fibula-see **Fig. 3c**. At **4 years**, fibula resection was performed in the distal ¼ with 15 mm shortening and additional new braces were applied to correct varosity in the supracondylar region of both femurs – see **Fig. 4a–d**. However, these were no longer tolerated and treatment was discontinued at 7 years. At the age of **8 years**, due to anterolateral curvature and varosity in the distal third of both tibias, a two-level osteotomy of both tibias, osteotomy of the fibula in the distal quarter and intra-articular fixation of both tibias with Küntscher nails were performed (at the orthopaedic-traumatology department of the hospital in Pribram). Healing of ostetomies of both tibias was demonstrated by X-ray examination in 5 months. Küntscher nails were extracted at 9.5 years.

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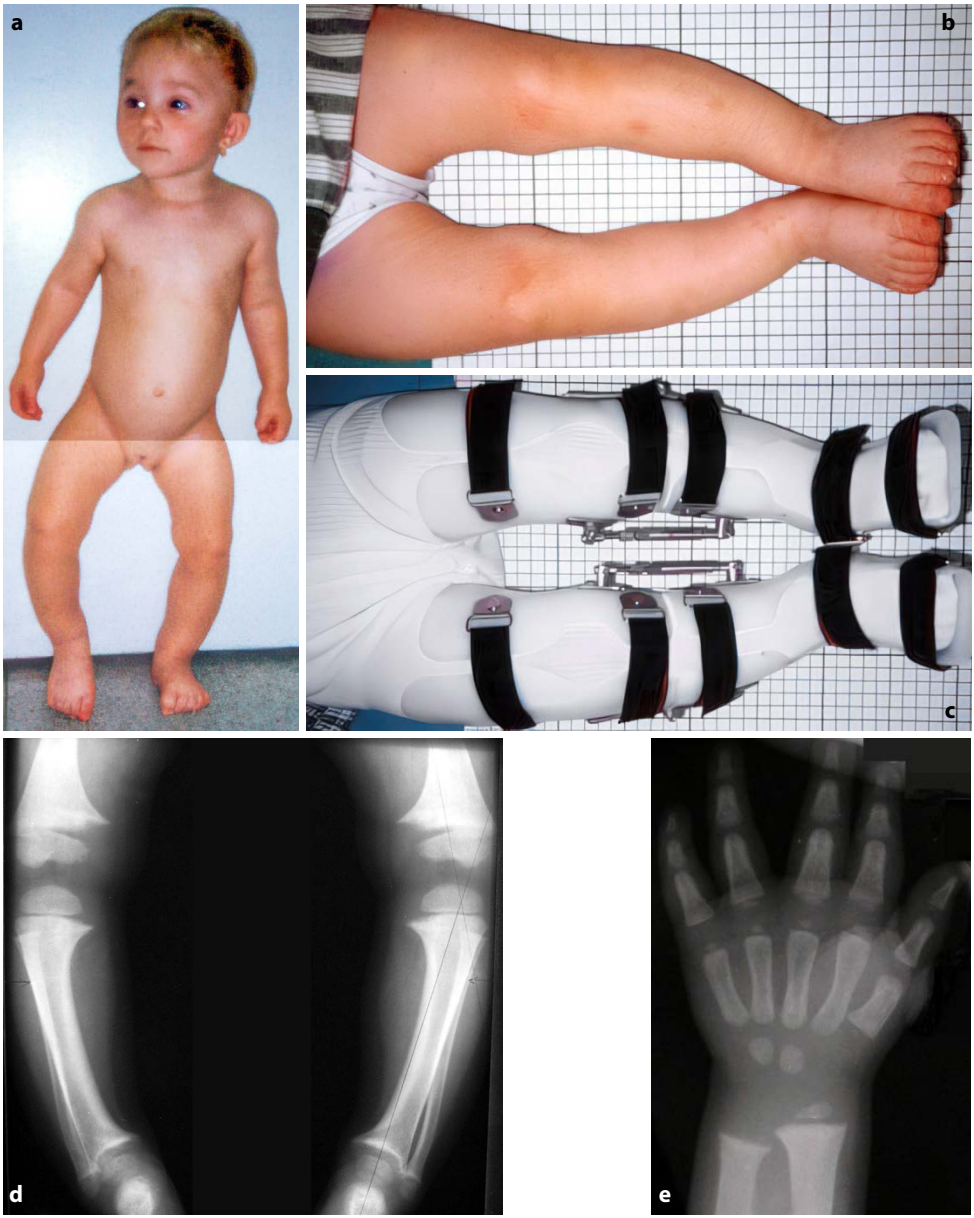


Fig. 2a–e. a. phenotype of **a girl at 2 years** with varosity of the knees and shanks; **b.** intercondylar distance in lying 5 cm; **c.** orthoses of lower limbs with bending pre-stressing; correction of varosity is at the level of the proxoimal tibia; **d.** X-rays of shanks and left hand at 20 months. Tibio-femoral angle is bilaterally about -28°; flaring of metaphyses at knee joint areas, varosity and cupping of the distal tibia metaphyses; overgrowth of fibula bilaterally; **e**. rachitic changes on the hand. The cortical thinning of the metacarpals and phalanges, slightly cupped distal metaphysis of ulna and radius.

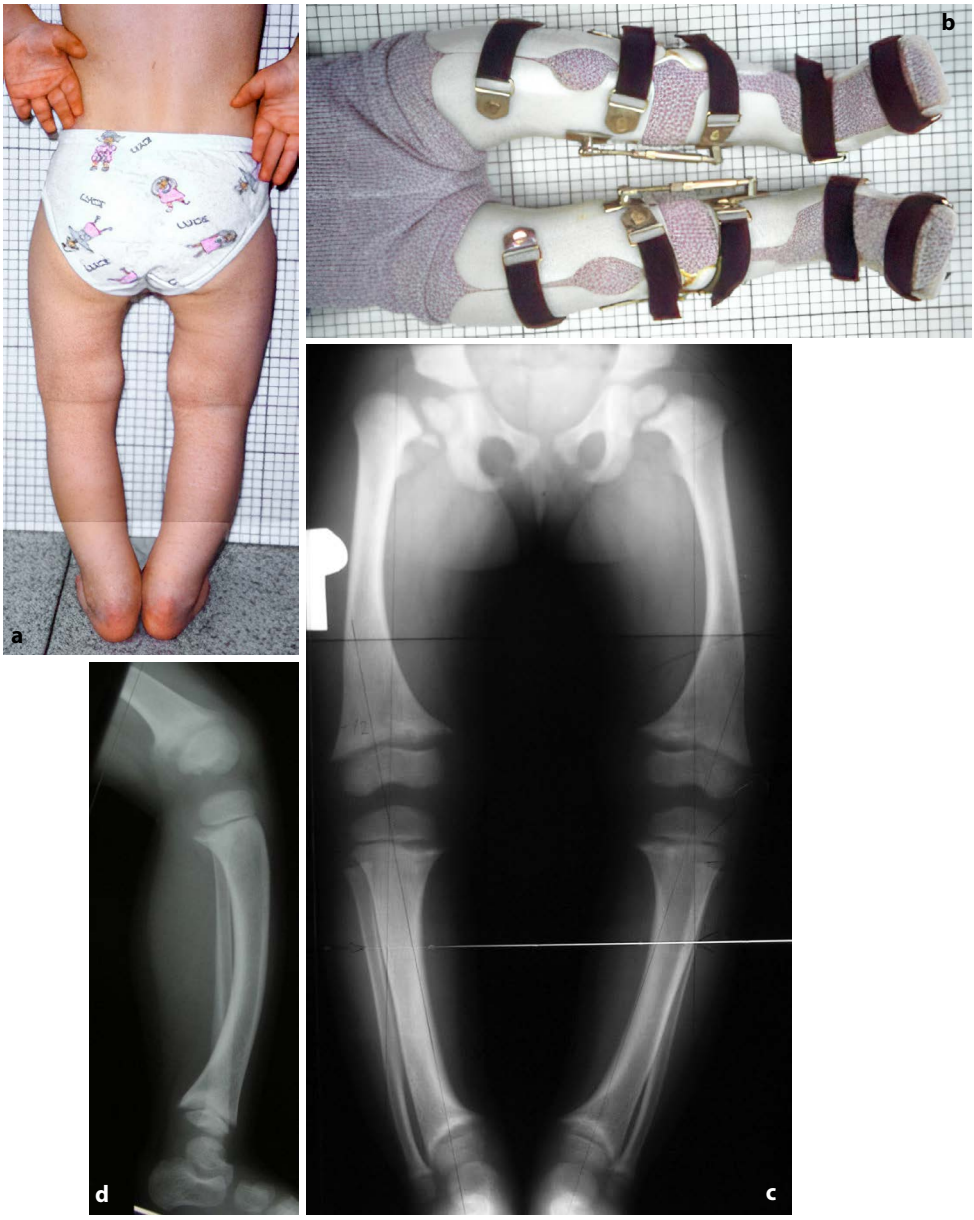


Fig. 3a–d. a. standing lower limbs from the back of a girl at **3 years**, see short upper limbs, intercondylar distance 4 cm, in supine position it was 3 cm; **b**. new lower limb braces with flexion preload in frontal plane; **c**. standing lower limb tele-radiograph: tibiofemoral angle right/left is 3°/4°; note the bilateral varosity of the femoral necks, bilateral varosity of the supracondylar and supramalleolar areas, marked overgrowth of the distal ends of both fibulae, enlargement of the zone of provisional calcification and metaphyses, and cup-shaped distal tibial metaphyses; **d**. ventral bowing of the tibia and typical rachitic changes.

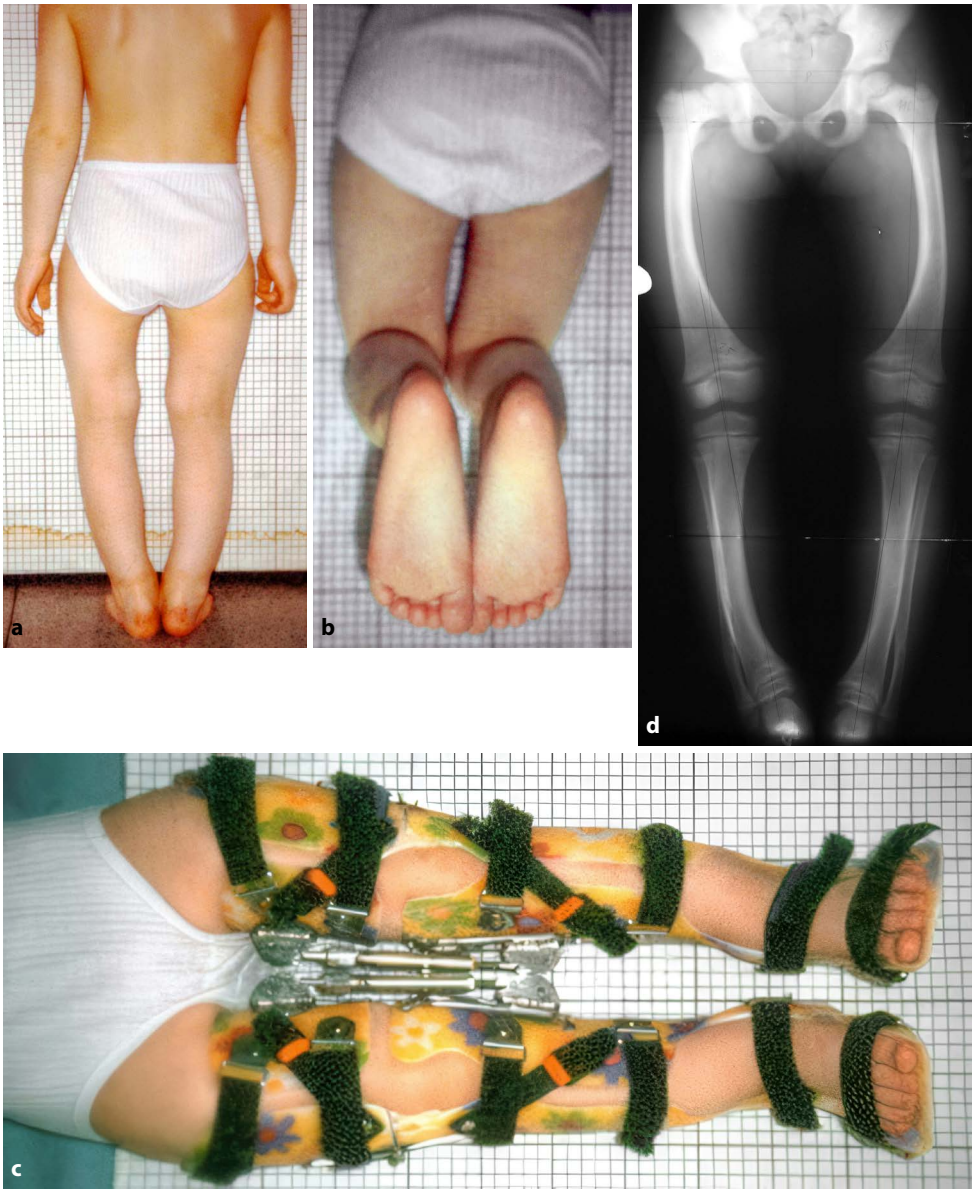


Fig. 4a–d. a. lower limbs from behind in standing position in a **girl at the age of 5 years**, intercondylar distance 2.8 cm, lying down 2.5 cm; **b**. internal tibial torsion approx. 5°; **c**. fitting of lower limbs with new orthoses with preload in the frontal plane after fibula resection in the distal 1/3 with shortening (performed at the age of 4 years; note that the correction of varosity is at the level of the supracondylar region; **d**. tele-radiography of the lower limbs in standing at 5.3 years: tibiofemoral angle right/left 5°/6°; varosity of both lower limbs is similar to that at 3 years, but rachitic changes are less pronounced. The shortening osteotomy of the distal fibula is completely remodelled bilaterally, but overgrowth is again present.

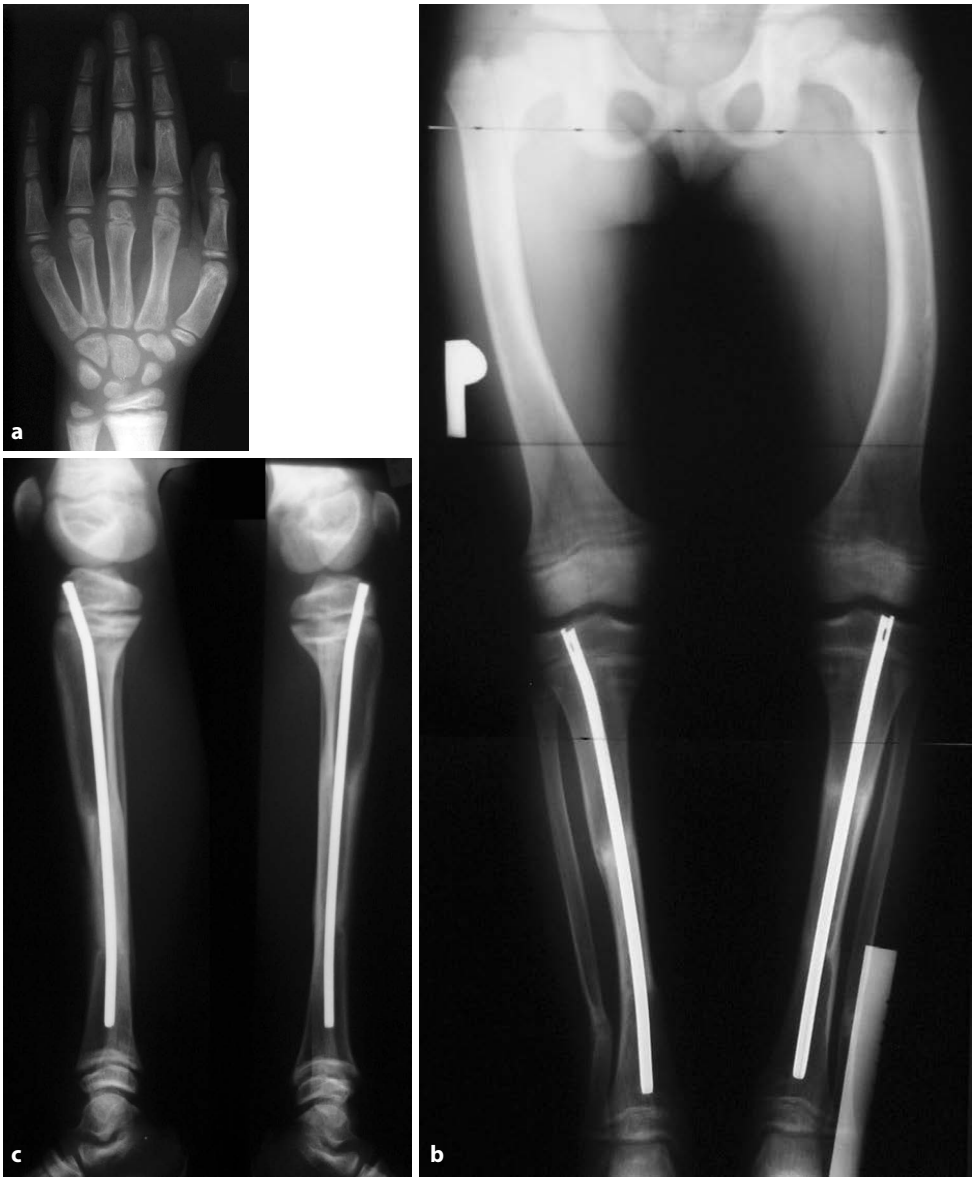
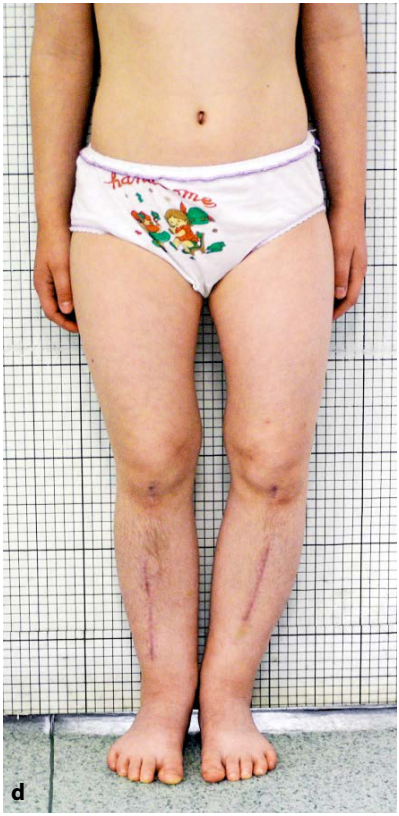


Fig. 5a–e. At **8 years of age**, corrective osteotomy of both tibias was performed for anterolateral curvature and varus in the distal third of both tibias: **a**. mild rachitic changes on left hand radiograph, bone age is delayed; **b, c**. teleroentgenogram of the lower extremities in AP projection in standing and lateral projection images of both tibias 5 months after surgery show very good remodeling of the two-level osteotomy of both tibias (fixed with Küntscher nails) and the fibula in the distal quarter; mild rachitic changes are present in all images; **d**, **e**. (next page) Anterior and posterior photographs of the lower limbs in standing position document, in agreement with the standing radiograph – see **b**, shortening of the right lower limb by 1 cm and varosity of the left knee joint predominantly in the supracondylar region of the left femur.



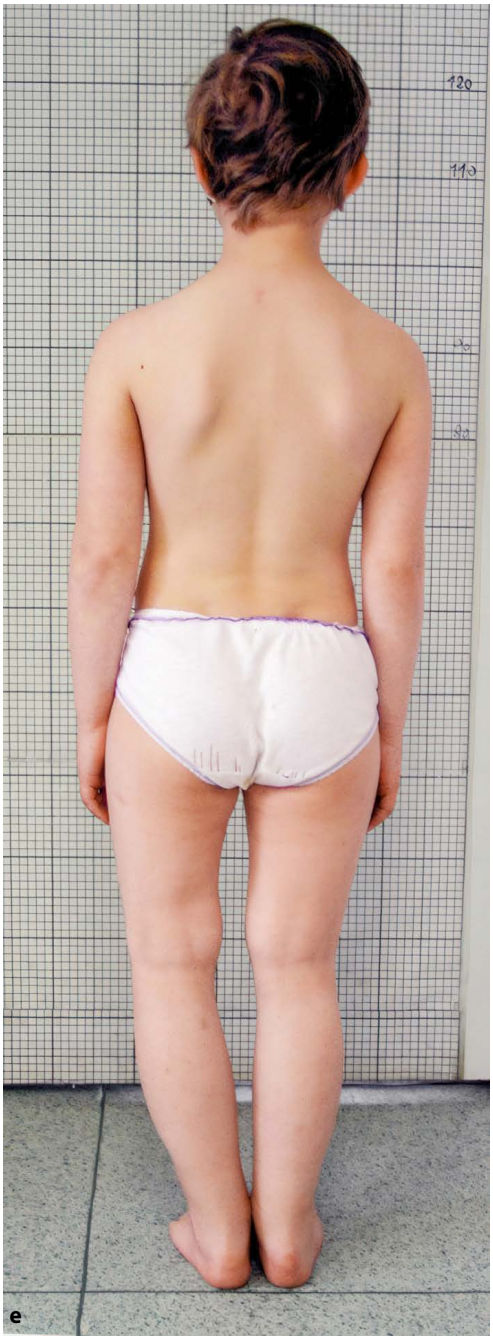


Fig. 5a–e. At **8 years of age**, corrective osteotomy of both tibias was performed for anterolateral curvature and varus in the distal third of both tibias: **d**, **e**. Anterior and posterior photographs of the lower limbs in standing position document shortening of the right lower limb by 1 cm and varosity of the left knee joint predominantly in the supracondylar region of the left femur.

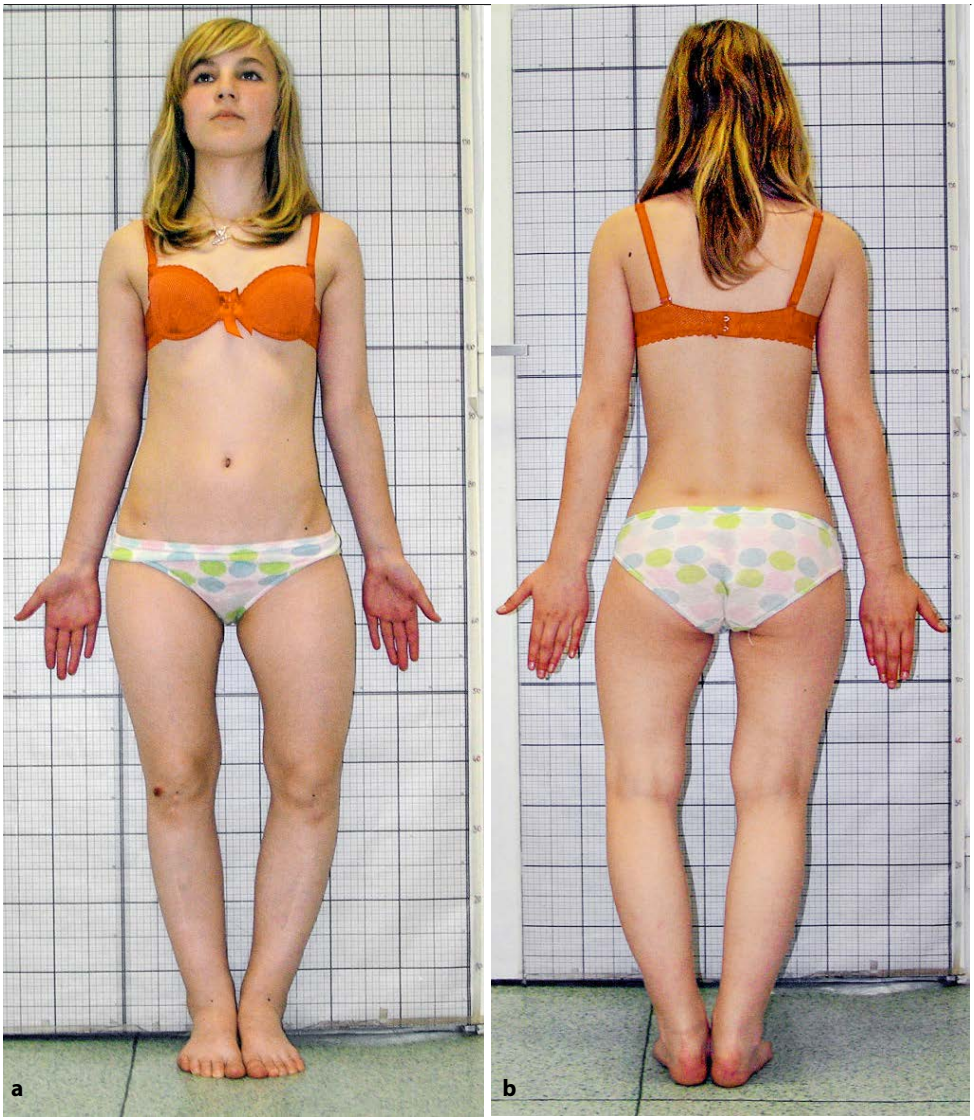


Fig. 6a–d. Phenotype of a **14-year-old girl**: **a**, **b**. front and back standing.

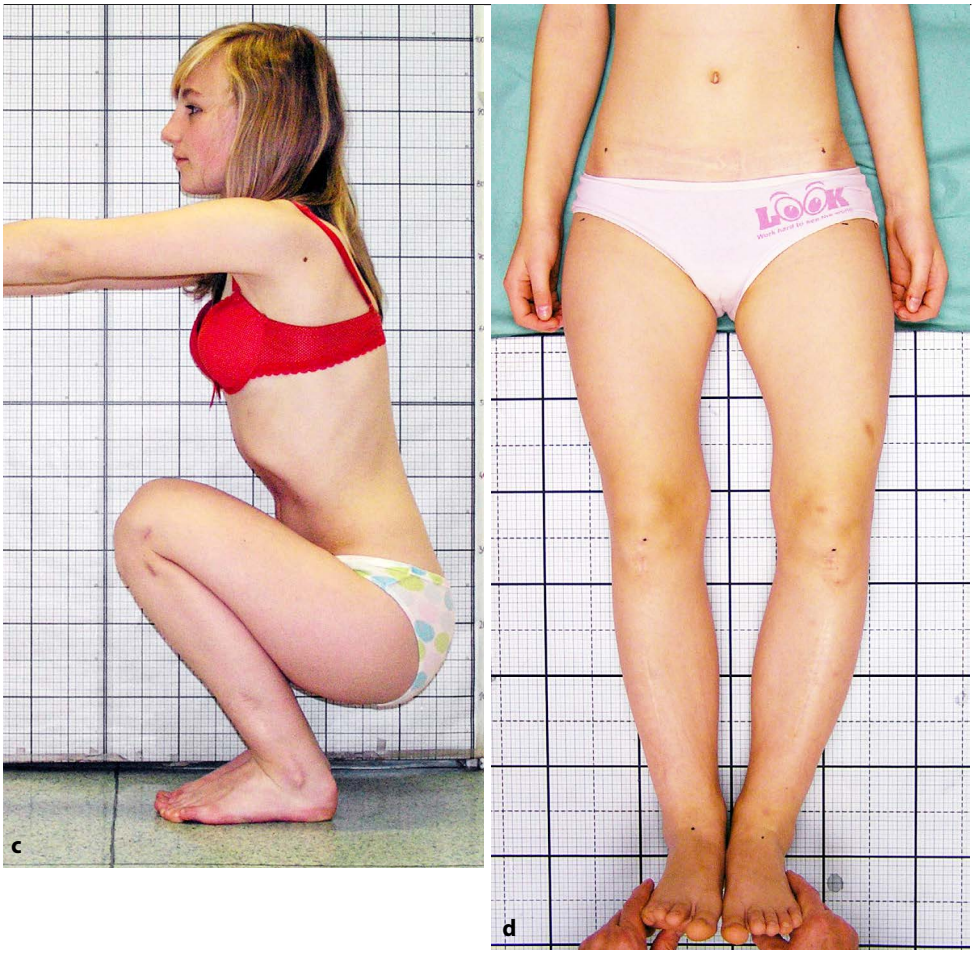


Fig. 6a–d. Phenotype of a **14-year-old girl**: **c**. squatting from the left; **d**. lower limbs lying down. Varosity is more evident in the left knee area. The inner condyle of the left femur deviates **4 cm** from the vertical, the right **2 cm**.

At the age of **13 years and 3 months**, at a bone age of 11.5 years for residual varosity of the proximal tibia of the left lower extremity, the girl was indicated for lateral drilling hemi-epiphysis in the left knee region. However, the remnant growth in the knee region was much lower than would be consistent with bone age, and menarche developed soon after surgery. Therefore, the operation did not have the expected effect. The planned valgus and external rotation osteotomy of the left proximal tibia was not performed due to the disagreement of one of the parents. The phenotype of the patient at **14 years** of age is shown in **Fig. 6a–c**.

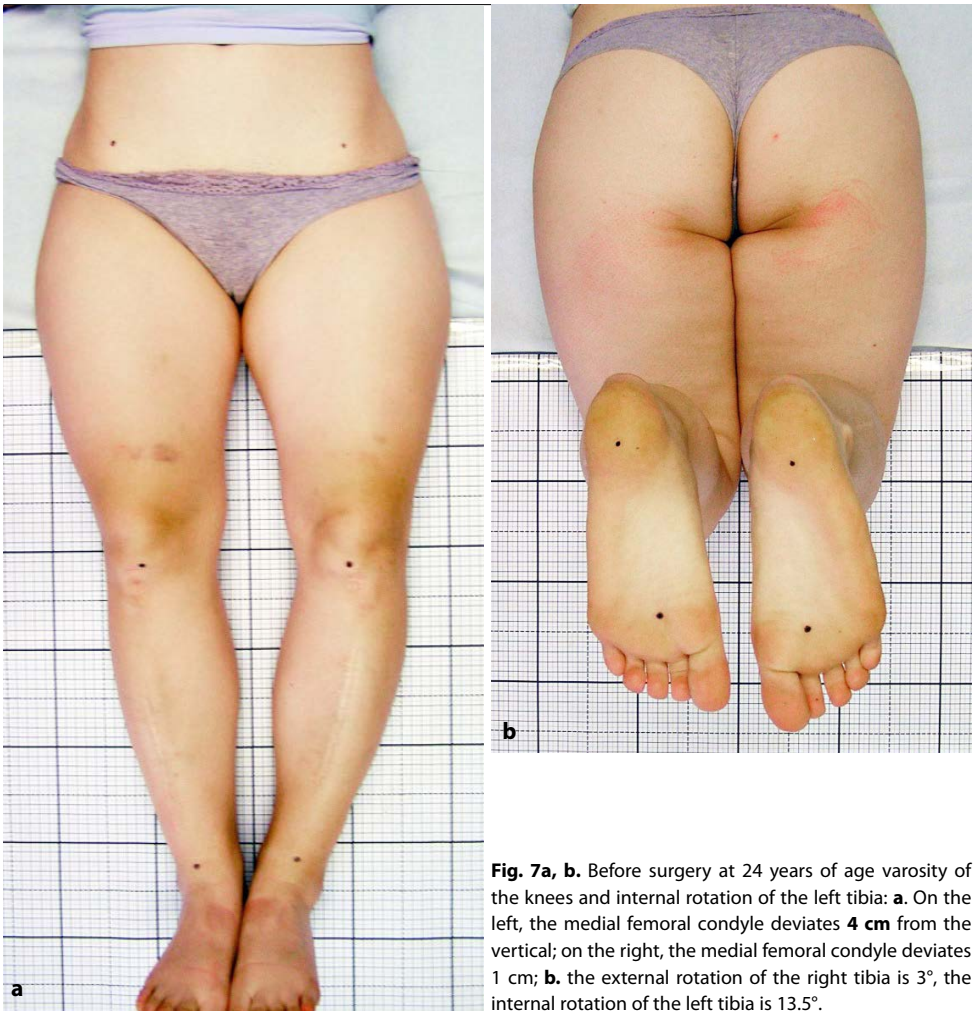


Fig. 7a, b. Before surgery at 24 years of age varosity of the knees and internal rotation of the left tibia: **a**. On the left, the medial femoral condyle deviates **4 cm** from the vertical; on the right, the medial femoral condyle deviates 1 cm; **b.** the external rotation of the right tibia is 3°, the internal rotation of the left tibia is 13.5°.

At the **age of 24**, the patient presented for a follow-up examination with a request to perform a surgery planned in childhood. After graduating from secondary vocational school, the patient works as a teaching assistant in Turnov. She is studying at the University of Technology in Liberec, specializing in social pedagogy. She is involved in firefighting.

She complains of pain in both knees after heavy loads, a wobbly gait with limping on the left lower limb and increased fatigue, which limits her in normal activities. She reports no problems with her dentition. She is bothered by a deformity of her left tibia.

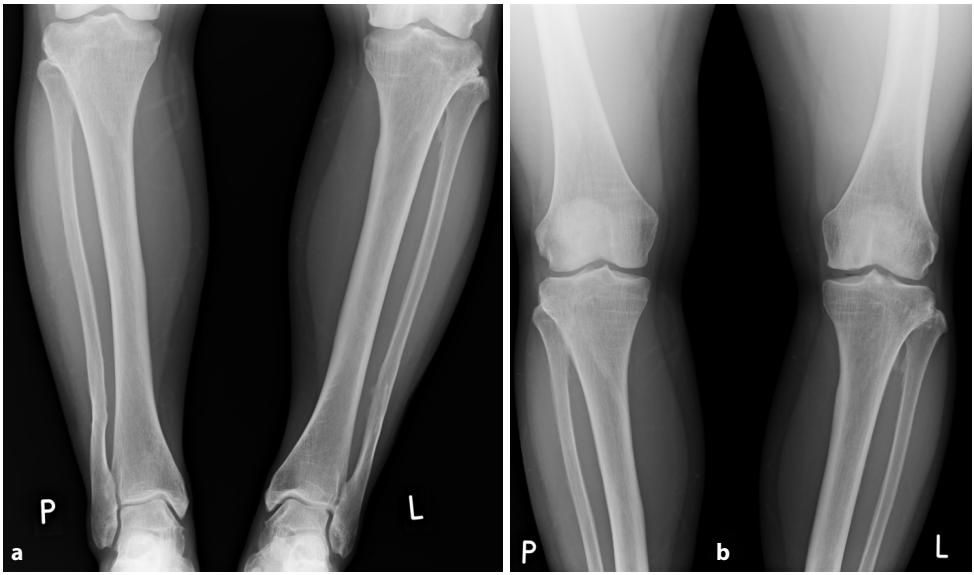


Fig. 8a, b. X-ray of both tibias and knees in anteroposterior projection – **24 years old - before surgery**: left tibiofemoral joint inclination is 8°; right articular slot is horizontal; varosity of the proximal dia-metaphysis of the left tibia is 5°; slight varosity in the distal 1/3 of the diaphysis of the femur bilaterally, more to the left. The articular slot of the talocrural joints are laterally varus – see **a**, more so on the left. Fine growth strips, so-called Harris lines, are shown on the condyles of both tibias medially.

The patient reached a body height of 149 cm (-2.9 SD), weight 52.6 kg, BMI 23.7. Sitting height 86.5 cm (-0.5 SD), significant shortening of the limbs: subischial length of lower limbs 62.5 cm (-3.6 SD), length of upper limbs 64.1 cm (-2.3 SD), arm span 155.5 cm. The gait is wobbly, squatting on the whole foot, rising without rebound. Asymmetric varosity of the tibiae is shown in **Fig. 7a** . In the hips, internal rotation of the right/left is 60°/70°, external rotation of the righ/left 30°/20°. The asymmetric torsion of the tibiae is shown in **Fig. 7b**. X-ray of both knees and tibiae shows **Fig. 8a, b**.

The pelvis is horizontal when standing, more inclined forward. The spine does not deviate, it develops smoothly in flexion, forward bend - the fingers of the hands on the ground. When extending lying on the stomach, the thoracic region develops less. The cervical spine is mobile without restrictions in the examined components of movement.

Abdominal and renal ultrasound (11.8.2022) was normal and showed no calcifications, lithiasis, congestion or nephrocalcinosis.

DEXA densitometric findings were within the average of the young adult norm, above the average age norm. Bone mineral density (BMD) in the lumbar spine is inhomogeneous, overestimated by degenerative changes.

Medication, surgery and post-operative course

The first author of the paper, based on his own experience with conventional and surgical treatment of 29 patients with XLH rickets and recent literature findings, conditioned the planned elective corrective surgery of the patient's left tibial deformity on the necessary normalization of the calciophosphate metabolism disorder and skeletal remodeling by the application of the drug Crysvita (bursumab).

The health insurance company approved the required treatment for a period of 6 months.

Burosumab (Crysvita inj. 30 mg in 1 mL) was administered 3 weeks prior to elective surgery (12.10.2023). The last application was on 21.3.2024. No adverse effects were observed after the application.

Biochemical examination was performed before and after surgery at the Institute of Rheumatology, Department of Clinical Biochemistry and Haematology, Prague 2. The values of the monitored biochemical markers before the introduction of treatment, during the 6-month treatment period and after discontinuation of treatment are shown in **Table 1**.

On 6.11.23 in the Regional Hospital in Pribram, a planned operation was performed – osteotomy of the left tibia and fibula in the proximal diametaphysis of the tibia with 10° valgus and 15–20° external rotation of the peripheral fragment, internal fixation of the LCP with an eight-hole splint. Postoperatively, the left lower limb was fixed with a rigid orthosis (20° semiflexion). Surgery and postoperative course was without complications. She was discharged on the third day after surgery.

Marker	P	ALP whole	CTX	P1NP	Osteocalcin	ALP bone	Calcidiol	Calcitriol
reference values	0.81–1.45	0.8–1.74	0.148–0.967	15.13–58.59	6.5–42.3	5.5–24.6	50.0–200	47.76–190.32
units	mmol/l	µkat/l	µg/l	µg/l	µg/l	ukat/l	nmol/l	pmol/l
date of samplig								
08.08.2022	0.63	3.31	1.32	165.8	38.7	66.7	87.3	125
16.08.2023	0.56	2.98	1.2	172.8			54.7	142
23.11.2023	0.82	3.52	2.18	199.8			46.9	66.7
21.12.2023	0.92	3.16	1.71	252	41.1	53.2	53.2	79.7
25.01.2024	0.84	2.67	1.14	204.1	36.4	48.8	77	111
22.02.2024	0.88	2.50	1.56	215	39	47.5	75.7	126
21.03.2024	0.84	2.43	1.33	222.50	34.80	47.40	62,.0	140.00
30.05.2024	0.55	2.73	1.09	110.00	28.30	57.40	59.70	
29.08.2024	0.45	3.10	0.632	114.00	36.8	57.0	90.5	

Table 1. Comparison of selected biochemical markers

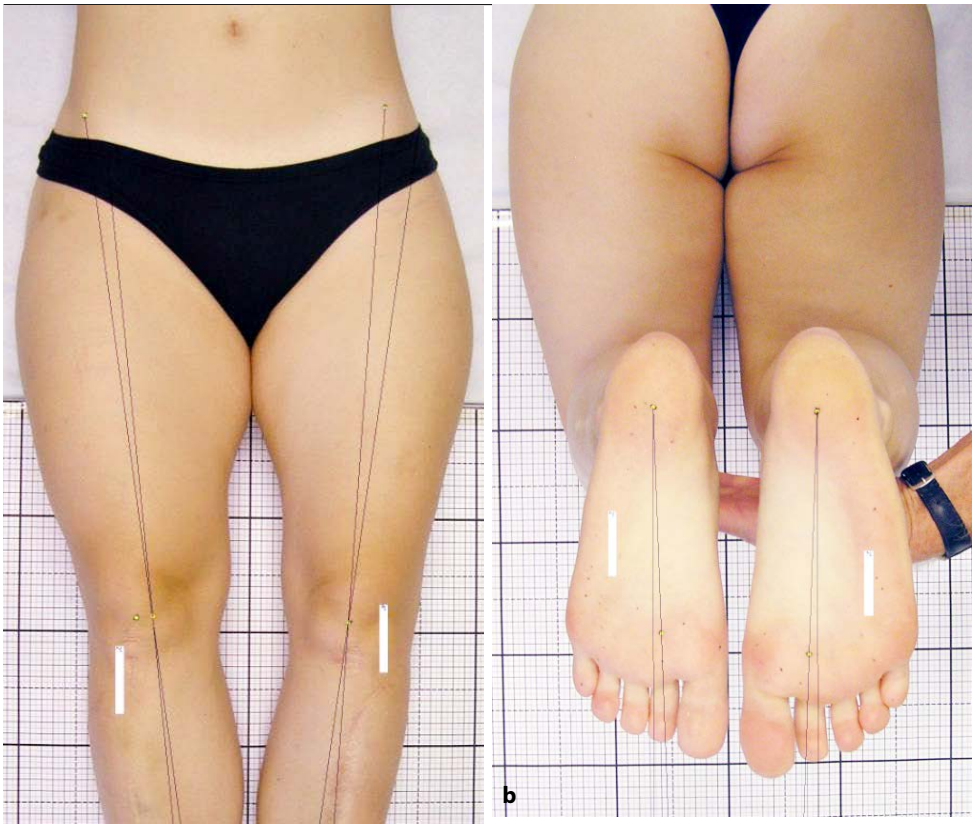
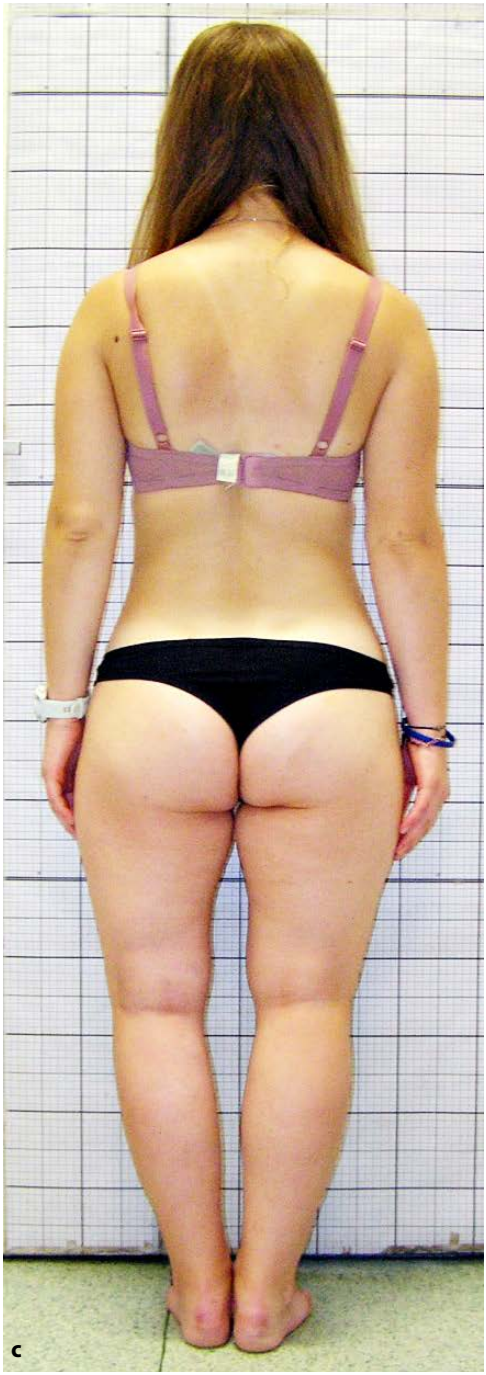


Fig. 9a–c. **After surgery** at **26 years**: **a**, **c**. small stature, shorter lower limbs, slight varosity in knees persists, now without evident asymmetry – on the left, the medial femoral condyle deviates 2.5 cm from the vertical; on the right, the medial femoral condyle deviates 1.5 cm); **b**. the symmetrical internal rotation of both tibia is 2°.

Further follow-up and treatment was conducted at the Centre for Defects of Locomotor Apparatus in Prague. Two weeks after the operation, the patient complained of pain in the sole of the left foot at night, hypesthesia of the thumb and sole of the foot and limitation of movement of the thumb and toes of the left foot. She was advised to walk with two French canes and left lower limb weight bearing, prescribed a knee brace (Playmaker xpert wrap) and rehabilitation. Medication vitamin D (2000 UI/day), Milgamma tbl. (vitamin B12 and B6), Aescin and Neurontin tbl.



The result of the operation can be seen in **Fig. 9a–c**.

After the operation, we observed a gradual decrease in the difficulties, namely pain in the left foot and toe. Four months after surgery (6 February 2024), full range of motion of flexion and extension of the toes of the left foot was restored.

A one-month stay in Janské Lázně (8.4. to 6.5.2024), where she underwent *comprehensive rehabilitation treatment*, contributed to a significant improvement in her condition and the decline of her difficulties. There was an improvement in trunk activation, strengthening of abdominal muscles and left lower limb. The patient was instructed in self-therapy. It was recommended to continue regular exercise as instructed, outpatient rehabilitation (RHB), repeat spa treatment and subsequent inpatient RHB treatment at a specialist medical institute. At home, she already walks without support fully loading the left lower limb. Hypesthesia of the left plantar foot and plantar thumb area persists. He still uses French canes when walking outdoors.

On conventional treatment, the patient had low serum phosphorus levels and elevated total ALP and bone isoenzyme ALP levels. *In 1 month after the 1st dose of drug Crysvita, hypophosphatemia normalized.*

Calcium (total), parathormon (PTH), Vitamin D (total), osteocalcin and 1.25(OH)2 vitamin D levels were repeatedly within normal reference values.

Fig. 9c. **After surgery** at **26 years**: small stature, shorter lower limbs, slight varosity in knees persists, now without evident asymmetry.

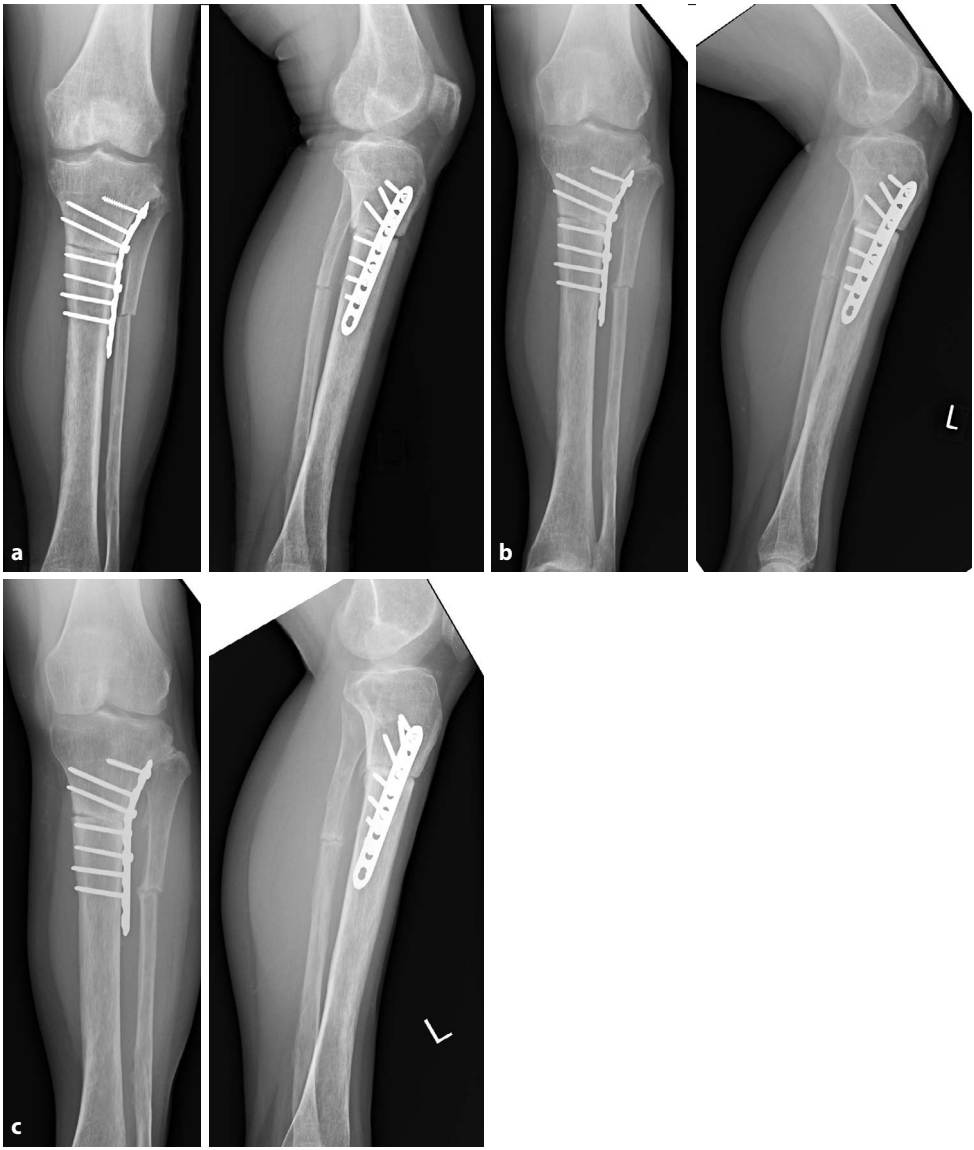


Fig. 10a–d. Correction and healing – remodeling of the tibia and fibula osteotomy: a, **b**. X-ray of the left tibia in anteroposterior and lateral projection **2.5 and 4.5 months after surgery**: the tibiofemoral angle and the slope of the knee joint slot is normal; the LCP splint and all screws are in situ without signs of loosening. Radiographic evidence of moderate continued remodeling (healing) of the tibia osteotomy – compare **a** and **b**; **c, d.** X-ray of the left tibia in anteroposterior and lateral projections **7 and 10 months after surgery**: the LCP splint and all screws are in situ with no signs of loosening; symmetric mild varosity of both knee and talocrural joints – see **d** (on the next page).

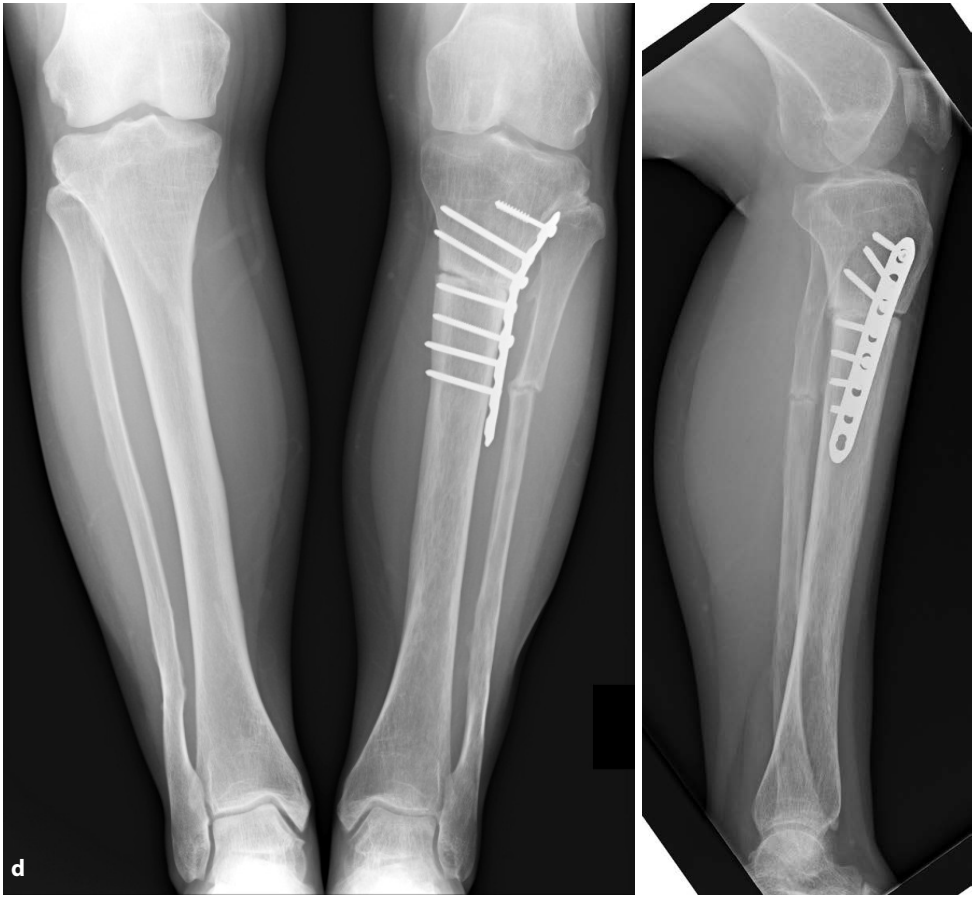


Fig. 10d. Correction and healing – remodeling of the tibia and fibula osteotomy 10 months after surgery: the LCP splint and all screws are in situ with no signs of loosening; symmetric mild varosity of both knee and talocrural joints; Radiographic evidence of moderate continued remodeling (healing) of the tibia osteotomy – compare **a** and **b**.

Treatment did not affect elevated total ALP, bone ALP isoenzyme, or elevated bone turnover markers (CTX and P1NP). These biochemical markers were elevated before administration of drug Crysvita, during and after treatment, as were total cholesterol and LDL cholesterol levels.

Two months after the end of treatment with burosumab (Crysvita), the patient's serum phosphorus levels were again low.

Bone healing – remodeling was monitored on X-ray images of the left tibia in two projections, see **Fig. 10a–d**. In the AP projection, the broader line of the osteotomy in the medial third shows

signs of remodeling, while the outer two thirds are already remodeled. In the lateral projection, remodeling of the osteotomy is present in the posterior 2/3, still lacking sufficient ossification of the ventral cortical bone muscle. Osteotomy of the fibula is interspersed with mineralizing muscle in both projections.

CONCLUSIONS

The authors present the outcome of early conventional treatment in a patient with XLH rickets from childhood to adulthood. They successfully corrected the varus deformities of the lower limbs with orthotic treatment in the preschool years. After discontinuation of orthotic treatment, due to intolerance, the tibial deformity was addressed with a two-level osteotomy of both tibiae at the end of the growth period with good results. A planned corrective osteotomy of the left tibia for residual varosity and internal torsion of the left tibia was not performed due to one parent‘s disagreement with surgery.

The current aim of the communication was to verify the transient compensation of calcium phosphate metabolism (normalization of hypophosphatemia) and to stimulate the healing of the osteotomy by the effect of 6 months of burosumab (Crysvita) administration. We have documented normalization of phosphatemia and favorable remodeling of the left tibial corrective osteotomy, which was performed in adulthood at the patient's request after insurance approval for elective surgery.

The result of 11-month follow-up of biochemical indices of bone metabolism and bone remodeling on X-ray images after surgery confirmed, in agreement with the literature, that burosumab (Crysvita) is a drug that compensates for hypophosphatemia during the period of administration, and leads to stimulation of bone healing, which is significantly impaired and prolonged in adult patients (with the risk of developing pseudoarthrosis).

Burosumab is currently the only drug that directly targets the underlying cause of the disease, i.e. elevated FGF23 levels, and is also the only treatment option that leads to compensation of calciophosphate metabolism and normalization of bone healing. According to current literature reports, no adverse effects have been observed with long-term administration of burosumab.

Our message: For sufficient healing of elective surgary or fracture in adults, it will be necessary to compensate bone metabolism by administration of burosumab for at least 12 month.

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Address for correspondence:

Professor Ivo Mařík, M.D., Ph.D.
Centre for Defects of Locomotor Apparatus l.l.c.
Olšanská 7, 130 00 Prague 3, Czech Republic
e-mail: ambul_centrum@volny.cz