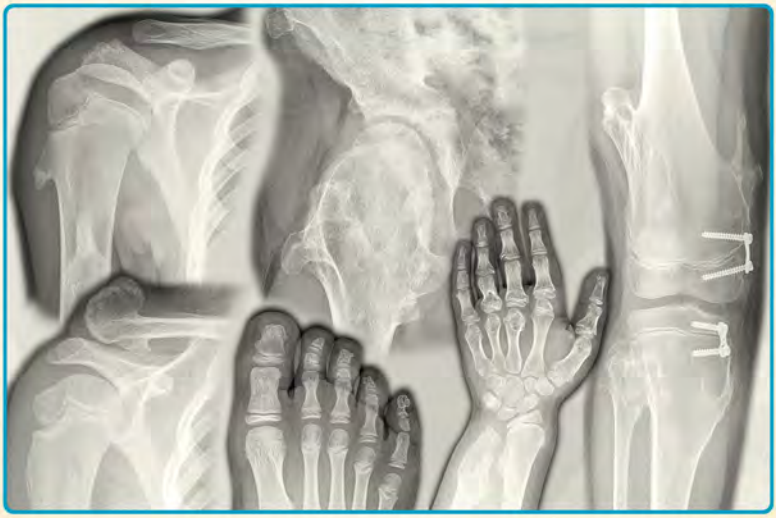
Pohybové ústrojí

Pokroky ve výzkumu, diagnostice a terapii



Vydává
Společnost pro pojivové tkáně ČLS J. E. Purkyně z.s.
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Ambulantní centrum pro vady pohybového aparátu, s.r.o.

ročník 29 / 2022 číslo 1

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ISSN 2336-4777

ORLING

ZALOŽENO ROKU 1992

BIOAKTIVNÍ KOLAGENNÍ PEPTIDY REGENERUJÍ

Kolagen je nezbytný pro pohyblivost kloubů, stabilitu kostí, odolnost a pevnost vazů a šlach a také pro zdravé svaly a hojně se vyskytuje i v cévách, meziobratlových ploténkách, hematoencefalické bariéře a rohovce, dentinu a střevní stěně – kolagen je životně důležitá složka celého těla.

Kolagenní peptidy zvyšují syntézu kloubního kolagenu a proteoglykanů

Nejen sportovci jsou ve zvýšené míře náchylní ke kloubním problémům a léčba se u nich nijak neliší od jejího zvládání u běžné populace. Hlavním cílem je minimalizovat bolestivost a zlepšit funkčnost kloubů. Klinická studie provedená v Penn State University testovala účinek kolagenních peptidů na studenty sportovních škol, kteří trpěli kloubními problémy v důsledku mechanické zátěže. V porovnání s kontrolní skupinou došlo u studentů, kteří užívali kolagenní peptidy, k **výraznému snížení kloubních potíží a také ke zlepšení pohyblivosti.** Tyto pozitivní účinky byly patrné zejména u účastníků s problémy kolenních kloubů pocházejících z mechanické zátěže. *(Clark K. , Sebastianelli W., Flechsenhar K., Aukermann D., Meza F., Millard R., Deitch J., Sherbondy P., Affiliations A., 24-Week study on the use of collagen hydrolysate as a dietary supplement in athletes with activity-related joint pain, Curr Med Res Opin, 2008 May;24(5):1485-96)*

Významný je i vliv kolagenních peptidů na hustotu kostí, zejména u osob s osteoporózou či osteopenií, potvrzeno už v roce 2010 pilotní studií s doplňkem stravy Calcidrink®.

V této studii se řešil „Vliv suplementace kolagenními peptidy, vápníkem a vitaminem D, resp. Calcidrinkem® na úbytek kostní hmoty a remodelaci kosti u postmenopauzálních žen s osteopenií“ *(Ortopedie 2010, Gabriela Šimková, Revmatologická ambulance 1. PP Kladno)*. Výsledky byly velmi nadějné. U žádné pacientky se nevyskytly během sledovaného období jednoho roku žádné nové nízkozátěžové zlomeniny. Cílem bylo prokázat účinek pravidelného užívání přípravku Calcidrink (vitamín D, kalcium a kolagenní peptidy) na snížení úbytku kostní hmoty u postmenopauzálních žen s osteopenií. Výsledky studie tento efekt potvrdily.

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Prof. MUDr. Milan Adam, DrSc. byl první, kdo objevil obrovský potenciál kolagenních peptidů a v průběhu let jej další vědci a lékaři opakovaně prokázali a ještě rozšířili oblasti použití, pro které jsou kolagenní peptidy vhodné.

Prof. MUDr. Milan Adam, DrSc. Dr.h.c.
český revmatolog, zakladatel kloubní výživy Geladrink®

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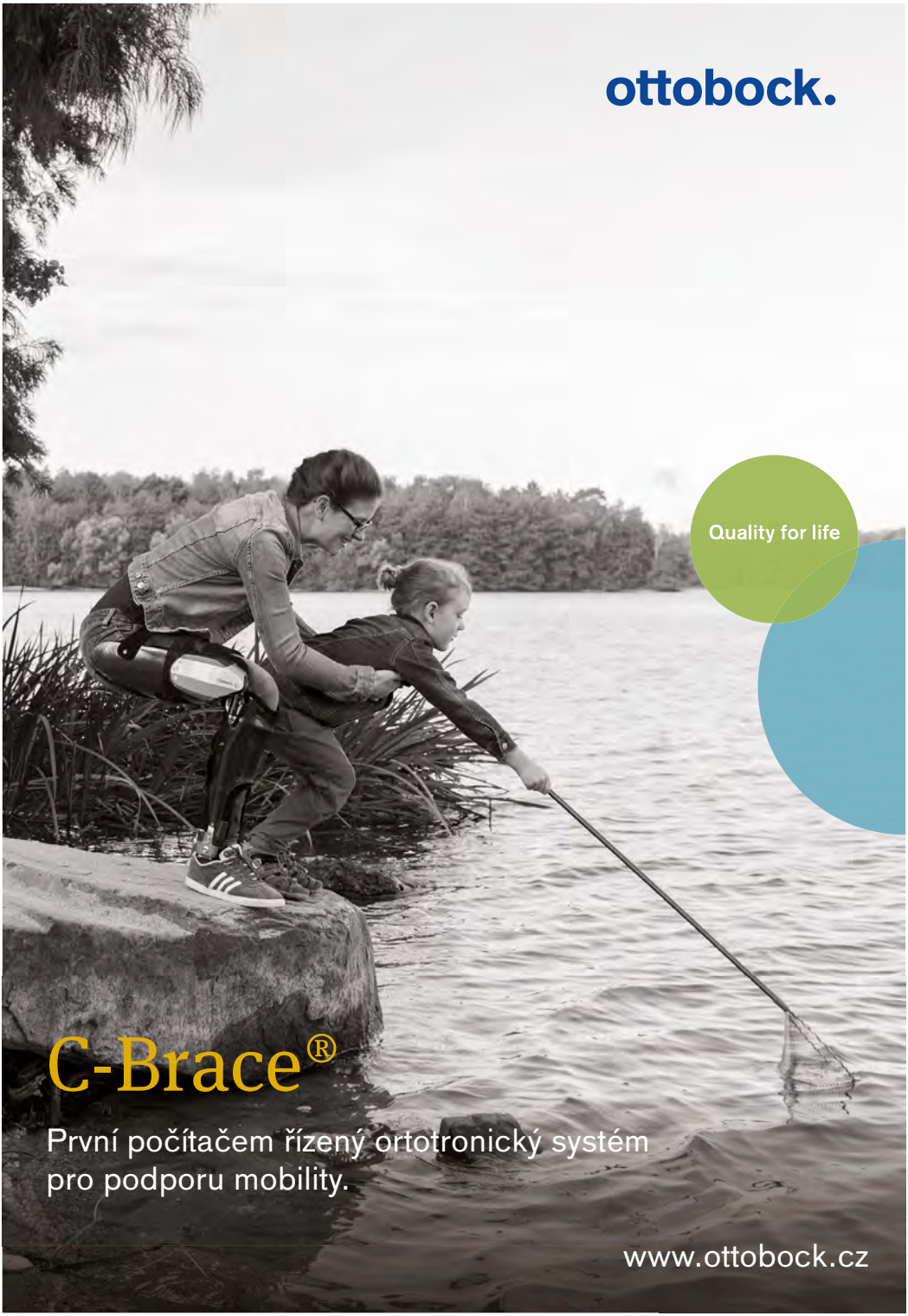
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ročník 29, 2022, číslo 1 | datum vydání: 29. 12. 2022

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Pohybové ústrojí. Pokroky ve výzkumu, diagnostice a terapii.

ISSN 2336-4777 (od roku 2013 pouze on-line verze)
Vydává Společnost pro pojivové tkáně ČLS J. E. Purkyně z.s.
& Ortopedicko-protetická společnost ČLS J. E. Purkyně z.s.
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Časopis je na Seznamu recenzovaných neimpaktovaných periodik vydávaných v České republice. Dvě čísla časopisu vycházejí v elektronické verzi jako ročník s průběžným vydáváním příspěvků po recenzi.
Při příležitosti sympozií je dvakrát ročně vydáváno supplementum.

Pro současné odběratele časopisu PÚ a další zájemce doporučujeme přihlásit se na http://www.pojivo.cz/en/newsletter/, zadat jméno a e-mailovou adresu, na kterou bude časopis posílán. Na webové doméně SPT ČLS JEP http://www.pojivo.cz/cz/pohybove-ustroji/ naleznete ve formátu PDF všechna jednotlivá čísla a dvojčísla časopisu (včetně Supplement) vydaná od roku 1997.
Rukopisy zasílejte na adresu *profesor MUDr. Ivo Mařík, CSc., Olšanská 7, 130 00 Praha 3, (ambul_centrum@volny.cz)* ve formátu doc. Vydavatel upozorňuje, že za obsah inzerce odpovídá výhradně inzerent. Časopis, jakožto nevýdělečný, neposkytuje honoráře za otištěné příspěvky.

LOCOMOTOR SYSTEM

Advances in Research, Diagnostics and Therapy

Published by The Society for Connective Tissues, Czech Medical Association of J. E. Purkyně, Prague, Society for Prosthetics and Orthotics, Czech Medical Association of J. E. Purkyně, Prague, Czech Republic and Centre for Defects of Locomotor Apparatus Prague, Czech Republic.

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Support this journal by sending in your best and most interesting papers. The issue of the journal is published during whole year after proof acceptation of the reviewers. In occasion of the symposia (twice a year) is published the supplement.

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Submitted papers: Locomotor System will review for publication manuscripts engaged in diagnostics and interdisciplinary treatment of genetic and metabolic skeletal disorders, limb anomalies, secondary osteoporosis, osteo/spondyloarthritis and another disorders that negatively influence development and quality of locomotor apparatus during human life. Both papers on progress in research of connective tissue diagnostics, medical and surgical therapy of multiple congenital abnormalities of skeleton mainly in the fields of paediatric orthopaedic surgery and plastic surgery, orthotics and prosthetics treatment, and papers dealing with biomechanics, clinical anthropology and paleopathology are appreciated.

The journal has an interdisciplinary character which gives possibilities for complex approach to the problems of locomotor system. The journal belongs to clinical, preclinical and theoretical medical branches which connect various up-to-date results and discoveries concerned with locomotor system. You can find the volumes of Locomotor System journal at http://www.pojivo.cz/cz/pohybove-ustroji/ since 1997 (free of charge). Since 2013 only electronic edition of the journal is available. That is why we recommend to all subscribers and those interested apply at http://www.pojivo.cz/en/newsletter, enter personal data, titles and e-mail address where the journal will be mailed.

Abstracts of presented papers are excerpted in EMBASE/Excerpta Medica (from the year 1994) and in the Bibliographia medica Čechoslovaca (from the year 2010). We prefer the manuscripts to be prepared according to Uniform Requirements for Manuscripts Submitted to Biomedical Journals (Vancouver Declaration, Brit med J 1988; 296, p. 401–405).

29. ročník časopisu Pohybové ústrojí – pokroky ve výzkumu, diagnostice a terapii je věnován jubilantům, členům Společnosti pro pojivové tkáně ČLS J.E. Purkyně a členům redakční rady časopisu

prof. Ing. Františkovi Maršíkovi, DrSc. – 80 let,
prof. MUDr. Štěpánovi Svačinovi, DrSc. – 70 let,
odb. asistentovi MUDr. Josefovi Krausovi, CSc. – 71 let
MUDr. Jiřímu Vosátkovi – 72 let
a odb. asistentovi Jackovi Karskimu, MD, Ph.D. – 59 let

The 29th volume of Locomotor System journal – Advances in Research, Diagnostics and Therapy is dedicated to jubilarians, members of the Society for Connective Tissues of the Czech Medical Association J.E. Purkyně and members of the Editorial Board of this journal

Professor Ing. František Maršík, DrSc – 80 years
Professor Štěpán Svačina, DrSc – 70 years
Assist. Professor Josef Kraus, PhD – 71 years
Jiří Vosátka – 72 years
and Assist. Professor Jacek Karski, MD, PhD – 59 years

**POHYBOVÉ ÚSTROJÍ –
POKROKY VE VÝZKUMU, DIAGNOSTICE A TERAPII, 29, 2022, č. 1**

Datum vydání: 29. 12. 2022

OBSAH

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Oznámení úmrtí

LOCOMOTOR SYSTEM – ADVANCES IN RESEARCH, DIAGNOSIS AND THERAPY, 29, 2022, No. 1

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SLOVO ČTENÁŘŮM

Vážení čtenáři, autoři a inzerenti!

Děkujeme za Vaši nezastupitelnou pomoc při tvorbě mezioborového odborného recenzovaného časopisu *„Pohybové ústrojí – pokroky ve výzkumu, diagnostice a terapii* (dále PÚ).“

Všechna čísla časopisu (včetně Supplement) vydaná od roku 1997 najdete ve formátu PDF na webové doméně Společnosti pro pojivové tkáně ČLS JEP z.s.
http://www.pojivo.cz/cz/pohybove-ustroji/ (bezplatný přístup).

Časopis PÚ byl v roce 2008 zařazen Radou pro výzkum, vývoj a inovace vlády ČR na Seznam recenzovaných neimpaktovaných periodik vydávaných v České republice. Od roku 2013 je časopis PÚ vydáván pouze v elektronické formě (v roce 2014 bylo přiděleno nové ISSN 2336-4777). V souvislosti se změnou v elektronickou formu vydávání v roce 2013 časopis nedopatřením vypadl z tohoto Seznamu. Od roku 2015 je elektronická forma Pohybového ústrojí opět na Seznamu recenzovaných neimpaktovaných periodik.

Od roku 2016 vydáváme v časopisu PÚ příspěvky přijaté po recenzi jako číslo 1 a 2, dále dvě Suplementa obsahující souhrny nebo abstrakta ze symposií Kubátovy dny a mezinárodního symposia.

Nedostatek příspěvků je příčinou zpožděného vydání i tohoto čísla 1 časopisu PÚ, 29, 2022. Příspěvky na vysoké odborné úrovni jsou v tomto čísle uveřejněny v anglickém jazyce. Čtenář nalezne poučení o tzv. metabolicky zdravé obezitě, geotermální vodě využívané k rehabilitaci pohybového ústrojí v Polsku, o diagnostice a symptomatickém léčení vzácných genetických chorob pohybového aparátu a o perspektivním léčení pacientů s XLH hypofosfatemickou křivicí rekombinantní lidskou IgG1 monoklonální protilátkou proti FGF23, které je dnes dostupné pro české děti a je nadějí i pro dospělé pacienty s přestavbovými zlomeninami dlouhých kostí.

V roce 2022 jsme opožděně vydali číslo 2 časopisu PÚ, 28, 2021. Suplementa 1 a 2 časopisu PÚ, 29, 2022 byla vydána souběžně s konáním zmíněných tradičních sympozií.

Při příležitosti 27. Kubátových dnů (téma Ortopedická protetika – mezioborová spolupráce 6 – kompenzace, které se konalo 12. března 2022 v Lékařském domě v Praze 2, byla předána ocenění jubilantům panu Ing. Františkovi Maršíkovi, DrSc. – 80 let, panu prof. MUDr. Štěpánovi Svačinovi, DrSc. (předseda České lékařské společnosti J. E. Purkyně z.s.) – 70 let, panu odb. asistentovi MUDr. Josefovi Krausovi, CSc. – 71 let a panu MUDr. Jiřímu Vosátkovi – 72 let. Odborné životopisy jubilantů jsou publikovány v Suplementu 1 časopisu PÚ, 28, 2021. V Suplementu 2 časopisu PÚ, 29, 2022 byla uveřejněna abstrakta z The 24th Prague-Lublin Symposium (topic Locomotor Apparatus Adaptation III – Interdisciplinary Aspects, November 5, 2022, Medical House, Sokolská 31, Prague, Czech Republic) a odborný životopis pana odborného asistenta Jacka Karskiho, MD, PhD (Lublin, Poland), který byl oceněn Čestnou medailí ČLS JEP a Diplomem Čestné členství v SPT ČLS JEP. Obě Symposia se konala

již osvědčenou prezenční a online formou jako v roce 2021, kdy z důvodu pandemie Covid-19 online forma plánovaných odborných akci umožnila jejich realizaci. Hybridní forma realizace symposií se nám osvědčila, obou sympozií uspořádaných v roce 2022 se zúčastnilo více než 200 účastníků.

Vedoucí redaktor časopisu PÚ navrhl přijmout mezi členy redakční rady prof. MUDr. Martina Krbce, CSc., přednostu Ortopedicko-traumatologické kliniky 3. LF UK a FNKV a vedoucího redaktora impaktovaného časopisu Acta Chirugiae Orthopedicae et traumatologiae Cechoslovaca. Pan profesor byl osobně dotázán, s členstvím souhlasí. Videozáznamy přednášek z 27. Kubátova dne, 23. Praha-Lublin-Sydney-St. Petersburg Symposia a 24. Praha-Lublin Symposia jsou k shlédnutí na webových stránkách www.pojivo.cz a www.ortoprotetika.cz.

Posláním časopisu PÚ je, jako v minulých letech, uveřejňovat vědecké práce zabývající se diagnostikou a mezioborovým léčením genetických kostních chorob, vrozených defektů končetin, sekundární osteoporózy, osteo/spondylartrózy, ale i jiných chorob, které ve svých důsledcích negativně ovlivňují růst, vývoj a kvalitu pohybového ústrojí v průběhu lidského života. Ceněny jsou práce vycházející z výzkumu pojivových tkání na všech úrovních poznání, práce orientované na biochemickou, morfologickou, genetickou a molekulární diagnostiku chorob pohybového ústrojí. Zvláštní pozornost je přikládána pracím z oblasti ortopedické a antropologické biomechaniky, neuroadaptačním změnám skeletu v období růstu, řízené remodelaci pojivových tkání, studiím muskuloskeletálních a neuronálních interakcí v závislosti na léčebných metodách (kalciotropní léky, rehabilitace, ortoticko-protetické a operační léčení aj.) a v neposlední řadě studiím antropologickým a paleopatologickým. Oceňujeme především interdisciplinárně zaměřené práce. V anglickém jazyce jsou publikována sdělení zahraničních i našich autorů. Žádaným doplněním obsahu časopisu jsou zprávy ze sjezdů a konferencí. Zveřejňujeme oznámení o životních výročích členů RR časopisu, SPT ČLS JEP z.s., OPS ČLS JEP z.s. a významných osobností, sdělením o prioritních pozorováních, ze studijních a poznávacích cest aj.

V každém ročníku najdete směrnice pro autory příspěvků, kterým věnujte prosím pozornost při tvorbě Vašich vědeckých sdělení. Souhrny prací publikovaných v časopisu jsou excerpovány v EMBASE / Excerpta Medica (od r. 1994) a v Bibliographia medica Čechoslovaca (od r. 2010).

K prosazení časopisu Pohybové ústrojí mezinárodně přispívá citovat práce publikované v našem časopisu v příspěvcích posílaných do zahraničních impaktovaných časopisů. Pro zvýšení mezinárodního zájmu o časopis PÚ je žádoucí publikovat původní kvalitní práce a kazuistiky v angličtině. Souhrny všech prací doporučujeme psát co nejvýstižněji, strukturovaně, česky a anglicky (objectives, methods, results and discussion), s klíčovými slovy.

Těšíme se na Vaši spolupráci a tvůrčí připomínky v roce 2023.

Redakční rada

A WORD TO READERS

Dear readers, authors and advertisers!

Thank you for your indispensable help in the creation of the interdisciplinary peer-reviewed journal *Locomotor System – Advances in Research, Diagnosis and Therapy* (journal LS).

All issues of the journal (including the Supplement) published since 1997 can be found in PDF format on the web domain of the Society for Connective Tissues of the Czech Medical Association J.E. Purkynje http://www.pojivo.cz/cz/pohybove-ustroji/ (free access).

In 2008, the journal was included by the Council for Research, Development and Innovation of the Government of the Czech Republic in the List of peer-reviewed non-impacted periodicals published in the Czech Republic. Since 2013, the journal has been published only in electronic form (in 2014, a new ISSN 2336-4777 was assigned). In connection with the change to electronic publication in 2013, the journal inadvertently dropped from this List. Since 2015, the electronic form of the journal Locomotor System is again on the List of peer-reviewed non-impacted journals.

Since 2016, we have been publishing papers accepted after peer review as Issues 1 and 2, as well as two Supplements containing summaries or abstracts from the Kubát Days and International Symposia.

The lack of contributions is the reason for the delayed publication of this issue 1 of the journal LS, 29, 2022. The contributions of a high professional level are published in this issue in English. The reader will find instruction on the so-called metabolically healthy obesity, geothermal water used for musculoskeletal rehabilitation in Poland, diagnosis and symptomatic treatment of rare genetic musculoskeletal diseases and the prospective treatment of patients with XLH hypophosphatemic rickets with recombinant human IgG1 monoclonal antibody against FGF23, which is now available for Czech children and is a hope for adult patients with stress bone fractures. In 2022, we belatedly published issue 2 of the journal PU, 28, 2021. Supplements 1 and 2 of the journal LS, 29, 2022 were published in parallel with the traditional symposia mentioned above.

On the occasion of the 27th Kubát Day (theme Orthopaedic Prosthetics – Interdisciplinary Cooperation 6 – Compensation, held on 12 March 2022 at the Medical House in Prague 2, awards were presented to jubilarians Mr. Ing František Maršík, DrSc. – 80 years, Mr. Prof. MUDr. Štěpán Svačina, DrSc. (President of the Czech Medical Association J. E. Purkyne /CMA JEP/) – 70 years, Mr. MUDr. Josef Kraus, CSc. – 71 years and Mr. MUDr. Jiří Vosátka – 72 years. The professional biographies of the jubilarians are published in Supplement 1 of the journal LS, 29, 2022. In Supplement 2 of the journal LS, 29, 2022 were published the abstracts of The 24th Prague-Lublin Symposium (topic Locomotor Apparatus Adaptation III – Interdisciplinary Aspects, November 5, 2022, Medical House, Sokolská 31, Prague, Czech Republic) and the professional curriculum of Mr. Assist. Professor Jacek Karski, MD, PhD (Lublin, Poland), who was awarded the Honorary Medal of the CMA JEP and the Diploma of Honorary Membership in the SCT CMA JEP. Both Symposia were held in the already proven presentational and online form as in 2021, when due to the Covid-19 pandemic the online form of the planned professional events made their implementation possible. The hybrid format of the symposia proved to be successful, with more than 200 participants attending both symposia.

The managing editor of the journal LS proposed to accept among the members of the editorial board Professor Martin Krbec, MD, PhD, Editor of the impacted journal Acta Chirugiae Orthopedicae et traumatologiae Cechoslovaca. The professor was personally asked if he agrees to the membership. Video recordings of lectures from the 27th Kubat's Day, The 23rd Prague-Lublin-Sydney-St. Petersburg Symposium and the 24th Prague-Lublin Symposium are available for viewing on the websites www.pojivo.cz and www.ortoprotetika.cz

The mission of the journal is to publish scientific papers dealing with the diagnosis and interdisciplinary treatment of genetic bone diseases, congenital defects of the limbs, secondary osteoporosis, osteo/spondylarthritis, as well as other diseases that adversely affect the growth, development and quality of the musculoskeletal system during human life. Works based on research on connective tissues at all levels of knowledge, works oriented on biochemical, morphological, genetic and molecular diagnostics of musculoskeletal diseases are valued.

Particular attention is paid to works in the field of orthopaedic and anthropological biomechanics, neuroadaptive changes of the skeleton during the growth period, controlled remodelling of connective tissues, studies of musculoskeletal and neuronal interactions in relation to therapeutic methods (calciotropic drugs, rehabilitation, orthotic-prosthetic and surgical treatment) and, last but not least, anthropological and palaeopathological communications. We particularly appreciate the interdisciplinary work. Communications by foreign and national authors are published in English. Reports from congresses and conferences are a welcome addition to the content of the journal. In the news section, we publish announcements of life anniversaries of members of the editorial board of the journal, Society for Connective Tissues CMA JEP & Society for Prosthetics and Orthotics CMA JEP and important personalities, announcements of priority observations, study and discovery trips, etc.

In each edition, you will find guidelines for authors of papers, which please pay attention to when drafting your scientific communications. Summaries of papers published in the journal are excerpted in EMBASE / Excerpta Medica (since 1994) and in Bibliographia medica Čechoslovaca (since 2010).

The citation of papers published in our journal in papers sent to foreign impacted journals contributes to the promotion of the journal Locomotor System internationally. In order to increase the international interest in the journal of Locomotor System, it is desirable to obtain original high quality papers and case reports in English. Abstracts of all papers are recommended to be written as concisely as possible, structured, in Czech and English (objectives, methods, results and discussion), with key words.

We look forward to your cooperation and creative comments in 2023.

Editorial Board

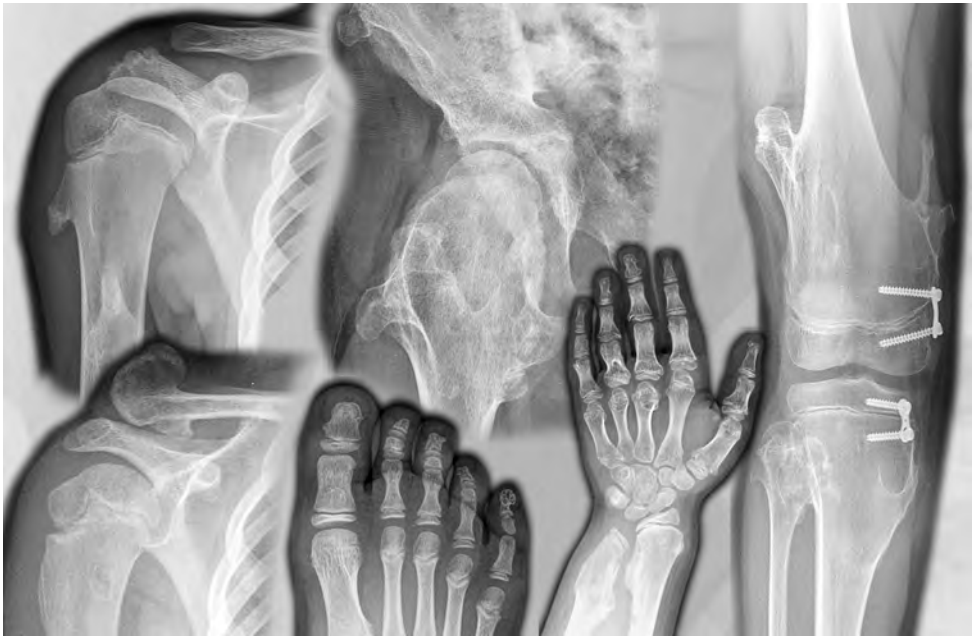
OBRÁZEK NA TITULNÍ STRANĚ ČASOPISU: MNOHOČETNÉ KARTILAGINOSNÍ EXOSTÓZY

OBRÁZEK NA TITULNÍ STRANĚ ČASOPISU časopisu (**obr. 1**) demonstruje typické rentgenologické obrazy a lokalizaci na skeletu u **Mnohočetných kartilaginosních exostóz (MCE)**. V literatuře se pro MCE užívají synonymní názvy: dědičné mnohočetné exostózy, diafyzární aklazie, exostózová chondrodysplazie, juvenilní osteokartilaginózní exostózy a mnohočetné exostózy typ I, II a III.

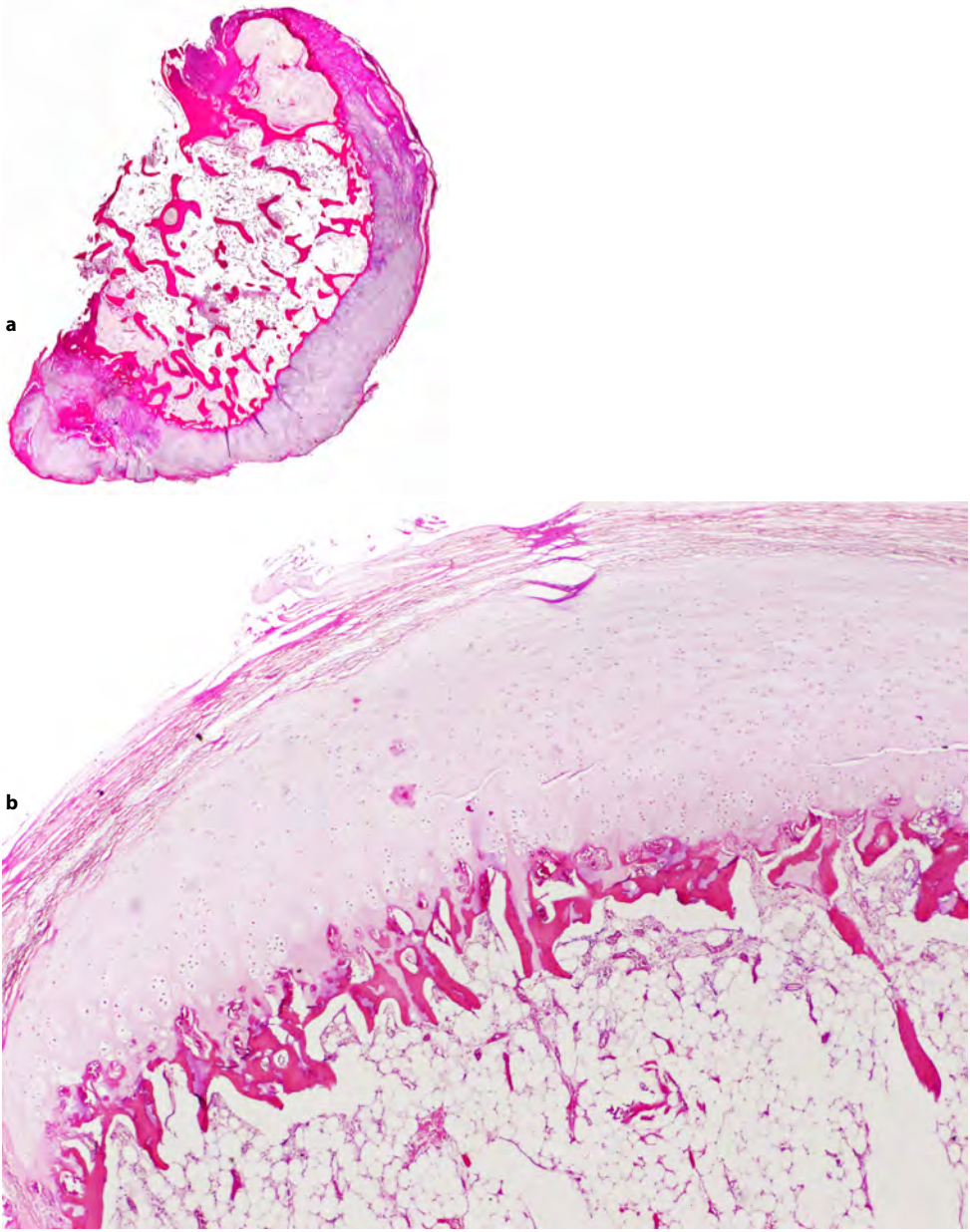
V 19. století několik typických případů popsal Virchow (**1876**). Volkov (**1972**) uvedl, že MEC je některými autory řazena mezi nádorům podobná onemocnění kostí a že byla zjištěna na vykopaných kostrách neolitického muže a lidoopa (Pithecanthropus).

Podle *Nosologie a klasifikace genetických kostních chorob: revise 2019* (**Mortier** et al. 2020) je MEC zařazena ve 29. skupině nazvané **Dezorganizovaný vývoj kostních komponent** (OMIM No. 133700, 133701, 600209, AD dědičnost, gen EXT1, EXT2, (609577) (609577) ORPHANET kód 321).

MCE je výsledkem vývojové poruchy epifyzární chrupavky (viz **obr. 2 a, b**). Kostní struktura uvnitř exostózy odpovídá spongióze a přímo přechází do spongiózy metafýzy. Kompakta exostózy rovněž přechází plynule v kompaktu dlouhé kosti. Na vrcholu exostózy se někdy prokazuje bezstrukturný



Obr. 1.



Obr. 2 a, b. Histologie: a) histotopogram osteochondromu, b) osteochondrom – zvětšeno 80x, HE. S laskavým svolením profesora MUDr. Ctibora Povýšila, DrSc.

vápenatý stín, odpovídající kalcifikované chrupavčité čepičce. Exostózy anebo sekundární deformity se obvykle pozorují do 12 let. Na RTG snímcích se zjišťují exostózy na rozšířených metafýzách, exostózy se s růstem zvětšují a migrují z metafýz do diafýz. Růst lézí se během adolescence zpomaluje a v dospělosti se nové léze neobjevují. Lokalizace kartilaginózních exostóz bývá polyostotická, polytopní a není symetrická. RTG obraz je pro diagnózu rozhodující.

Obrázek na titulní straně (**obr. 1**) je složen ze snímků obvyklých radiologických skeletálních znaků. MCE a typické expanze metafýz se vyskytují obvykle v oblasti kolenních kloubů a na horních koncích humerů, což jsou místa s největším růstovým potenciálem (**Spranger** et al. 1974, **Mařík** 2001): **vlevo nahoře a dole:** dvě exostózy *pravého proximálního humeru* – chlapec 13 let – a dvě exostózy *zevního konce pravého klíčku* – dívka 8 let. **Uprostřed dole**: *Prsty pravé nohy* – chlapec 9 let: hypoplazie středních článků 2.–5. prstu, drobné exostózy na distálním článku 1., 3.–5. prstu. *Levá ruka a zápěstí* – dívka 9,5 roku: uzavřená růstová fýza **základního článku 4. prstu a růstové** fýzy 3.–5. metakarpu, které jsou zkrácené. Rozšířené metafýzy základního a středního článku 3. prstu a středního článku 4. prstu, kde jsou patrné drobné exostózy. Ulna je distálně zkrácená a přihrocená, artikulace zápěstí je mezi radiem, os lunatum a navikulare. Exostózy mezi distálním koncem radia a ulny. **Uprostřed nahoře**: *pravý kyčelní kloub* – chlapec 13 let: difuzní expanze proximálního femuru, široký valgosní krček a plochá epifýza hlavice femuru; exostózy v okolí velkého a malého trochanteru, při zevním okraji acetabula a zevně od spina iliaca anterior superior. Lehká protruse acetabula do pánve. **Vpravo**: *pravé koleno* – chlapec 9,5 roku: difuzní expanze metafýz, přisedlé a stopkaté exostózy, osmičkové dlahy aplikované s cílem dočasné mediální hemi-epifyzeodézy a postupné korekce valgozity kolen.

Použity kopie RTG snímků z archivu Ambulantního centra pro vady pohybového aparátu s.r.o., Olšanská 7, 130 00 Praha 3.

Radiografické znaky

Pozorují se nepravidelně rozšířené metafýzy s přisedlými nebo stopkovitými výrůstky, které směřují k diafýzám dlouhých kostí. Postižené dlouhé kosti jsou často zkrácené, někdy se prokazuje tibiofibulární nebo radioulnární synostóza (častěji distální), která brání supinaci a pronaci předloktí. Distální konec ulny a proximální konec fibuly může být zkrácený, rozšířený nebo přihrocený. V kolenním a hlezenním kloubu pak vzniká valgózní deformita. Na prstech rukou či nohou se může vytvořit klinodaktylie nebo brachydaktylie. Exostózy se vyskytují i v plochých kostech, častěji podél crista ossis ilei a na vertebrálním okraji lopatky, na koncích klíčních kostí a na žebrech. Vzácně jsou na tělech obratlů, křížové kosti a dolní čelisti, nevyskytují se na klenbě lebky.

Klinické příznaky se projevují obvykle v prvních 10 letech. V predilekčních lokalizacích se zjišťují mnohotné tuhé výrůstky, někdy při palpaci bolestivé. Porušeným růstem dlouhých kostí dochází k asymetrickému zkrácení a zakřivení dlouhých kostí, ke kloubním deformitám s omezením rozsahu pohybu. Častá a typická je ulnární a volární deviace ruky označovaná jako Madelungova deformita, způsobená poruchou růstu distálního konce ulny osteochondromem (**Sprange**r et al., 2018, **Mařik**

2001). Analogická porucha růstu vzniká někdy na distálním konci fibuly a vede k biomechanicky závažné valgozitě a instabilitě horního hlezenního kloubu.

Dědičnost je AD se 100% penetrancí pro muže a menší penetrancí pro ženy. Vyšší incidence a těžší projevy ECH jsou u mužů. V jedné rodině je značně variabilní expresivita postižení, 1/3 případů se vyskytuje sporadicky.

Průměrná **incidence** se uvádí okolo 1 : 50 000 živě narozených dětí. Frekvence výskytu ale významně kolísá.

Etiopatogeneze

Většina případů MCE je způsobena mutacemi *EXT1* genu, který je lokalizován na chromosomu 8q24.11-q24.13 nebo *EXT2* genu na chromosomu 11p11-p12. Tyto geny kódují exostosin 1 a 2, transmembránové glykoproteiny, které katalyzují polymerizaci heparan sulfátu. Výsledkem mutací je ztráta tumorosní suprese. Exostózy vznikají u hetereozygotů po somatické mutaci druhé, funkční alely (ztráta heterozygosity). Maligní degenerace mnohočetných exostóz je způsobena mechanismy zahrnujícími jiné geny. Nejtěžší formy choroby a maligní transformace jsou sdruženy s mutacemi *EXT1*. Třetí gen způsobující MCE je umístěn na chromosomu 19p (**Le Merrer et** al., 1994, citováno podle **Sprange**r et al., 2018).

Průběh a prognóza

Průměrná výška mužů se uvádí 170 cm, žen 155 cm. Deformity, porucha kloubního rozsahu, centrace a disproporcionalita dlouhých kostí ovlivňují funkční postižení. V dospělosti se již exostózy nezvětšují a nové se netvoří. Exostózy mohou způsobovat útlak nervů (např. nervus peroneus communis), cév, míšních kořenů i míchy, vzácně mohou být příčinou obstrukce močových cest, střevní obstrukce nebo malpozice dělohy u těhotných. Byl popsán hemothorax u dvanáctileté dívky jako důsledek exostózy žebra (**Taybi a Lachman** 1996). Sarkomatózní degenerace se různými autory odhaduje na 2–10–20 % případů MCE. Podezřelé jsou rychle rostoucí, bolestivé exostózy v dospělosti. Nejčastěji v krajině kyčelního kloubu, proximálního konce humeru a v osteochondromech plochých kostí. Vzácně k malignizaci dochází před 10. rokem a po 50. roce života.

RTG známkou malignizace je ztráta kostní struktury, neostré ohraničení exostózy a rozpouštění kalcifikací v chrupavčité čepičce, kde se vyvíjí chondrosarkom. Při suspektní malignizaci indikujeme kostní scintigrafii, CT, MRI a ultrazvukové vyšetření (**Matějovský et al**. 1988). Životní prognóza je dobrá, pokud nedojde k malignizaci. Dispenzarizace postižených s ohledem na detekci prekancerotických změn je nutná po celý život. Významné se jeví zjišťování onkogenních markerů v dospělosti (**Mařík** 2001). Časné osteolytické změny lze zachytit monitorováním markerů osteoresorpce v moči (**Mařík et al**. 2000).

Léčení

Chirurgické odstranění exostóz se indikuje v případech, kdy exostózy způsobují bolest, omezení pohybu kloubu (exostóza může prorůstat do kloubní štěrbiny), uzuraci sousední kosti, či útlak nervů, cév a jiných měkkých tkání v okolí exostózy. Exostózy podezřelé z malignizace se musí ihned odstranit i s periostem a chrupavčitou čepičkou. Postižené jedince dispenzarizujeme jako prekancerózu, poučíme je o nutnosti sebepozorování. Madelungovu deformitu předloktí je možno řešit korekční osteotomií radia a prodloužením ulny (**Masada** et al. 1989). V období růstu desaxace kolen a hlezenních kloubů a nestejnou délku dolních končetin indikujeme k epifýzeodéze trvalé (návrtové) částečné či úplné. Timing výkonu řešíme ve spolupráci s antropologem. U desaxací v oblasti kolen a hlezen dnes preferujeme dočasnou hemi-epifýzeodézu s využitím osmičkových dlah. Po skončení růstu nestejnou délku (a současně i desaxce) je možné řešit prolongací končetiny pomocí zevního fixátoru (**Mařík 2001**) nebo korekčními osteotomiemi. Kostní remodelace při těchto výkonech je velmi dobrá (zkušenost autora).

Diferenciální diagnóza (**Taybi a Lachman** 1996):

1. Enchondromatóza se vyznačuje enchondromy v metakarpech (metatarzech) a falangách rukou (nohou), v metafýzách dlouhých kostí se rentgenologicky prokazují pruhovitá projasnění. Exostózy jsou malé a ojedinělé. Ojedinělé exostózy se nalézají i u případů metachondromatózy. Maffuciho syndrom se kromě mnohočetných enchondromů a ekchondromů projevuje mnohočetnými hemangiomy. U obou těchto generalizovaných chondromatóz je vysoké procento malignizace, a to v rozmezí 30–50 % (**Matějovský et al.** 1988). Jako Ollierova choroba se označuje enchondromatóza lokalizovaná na jednu končetinu nebo na polovinu těla.

2. Solitární osteochondromy se nedají rentgenologicky ani histologicky odlišit od mnohočetně se vyskytujících exostóz.

3. Exostózy se mohou vyvinout i u některých jiných kostních chorob a syndromů, např. u trichorinofalangeálního syndromu, typ 2 (Langer-Giedion), Turnerova syndromu, brachydaktylie typu E a XYY. Popisují se i koincidence hypochondroplazie nebo achondroplazie a mnohočetných exostóz. Exostózy byly zjištěny dále ve spojení s pseudohypoparathyreoidismem, morbus Legg-Calvé-Perthes, kardiopatií a ve spojení s mentální retardací, schizofrenií, Wilmsovým tumorem a pod.

4. Ojedinělé exostózy mohou být následkem mechanického dráždění periostu, subperiostálního poúrazového krvácení nebo periostitidy.

THE FIGURE ON THE TITLE PAGE OF THE JOURNAL: MULTIPLE CARTILAGINOUS EXOSTOSES

The figure on the title page of this journal demonstrates the typical radiological images and skeletal localization in **Multiple Cartilaginous Exostoses** (**MCE**). In the literature, synonymous names for MCE are used: *hereditary multiple exostoses, diaphyseal aclasia, exostosis chondrodysplasia, juvenile osteocartilaginous exostoses, and multiple exostoses types I, II, and III*.

In the 19th century, several typical cases were described by Virchow (9 – 1876). Volkov (10 – 1972) reported that MEC is classified by some authors as a tumor-like bone disease and that it has been found in excavated skeletons of Neolithic man and an ape (Pithecanthropus).

According to the Nosology and Classification of Genetic Bone Diseases: 2019 Revision (**12** – Mortier et al. 2020) MEC is classified in the 29th group called Disorganized development of skeletal components (OMIM No. 133700, 133701, 600209, AD inheritance, gene EXT1, EXT2, (609577) (609577) ORPHANET code 321, 321).

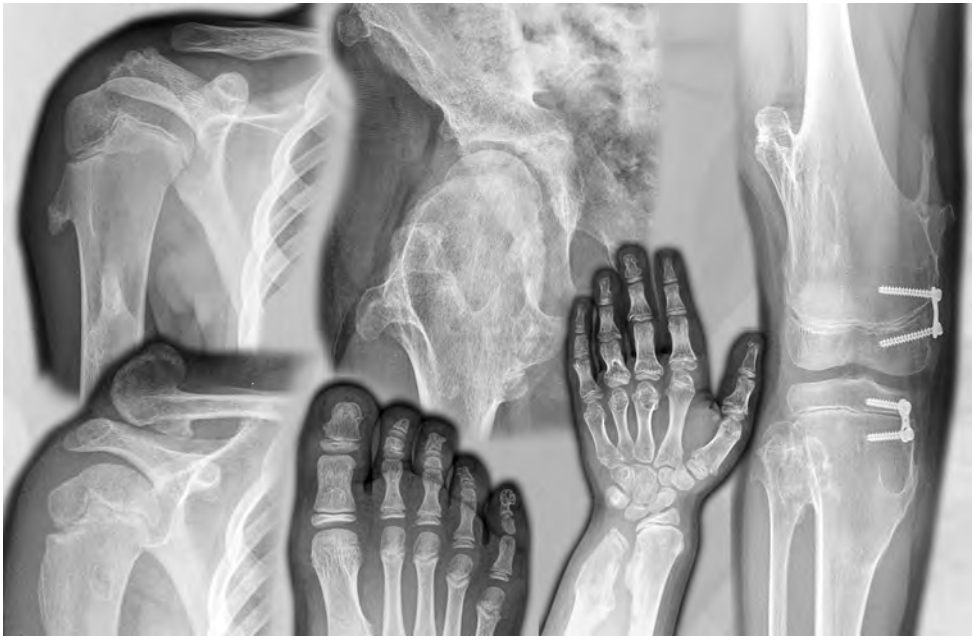


Figure 1. The cover image is composed of images of common radiological skeletal features. MCEs and typical metaphyseal expansions are usually found at the knee joints and at the upper ends of the humeri, the sites with the greatest growth potential (**Spranger et al. 2018**, **Mařík 2001**):

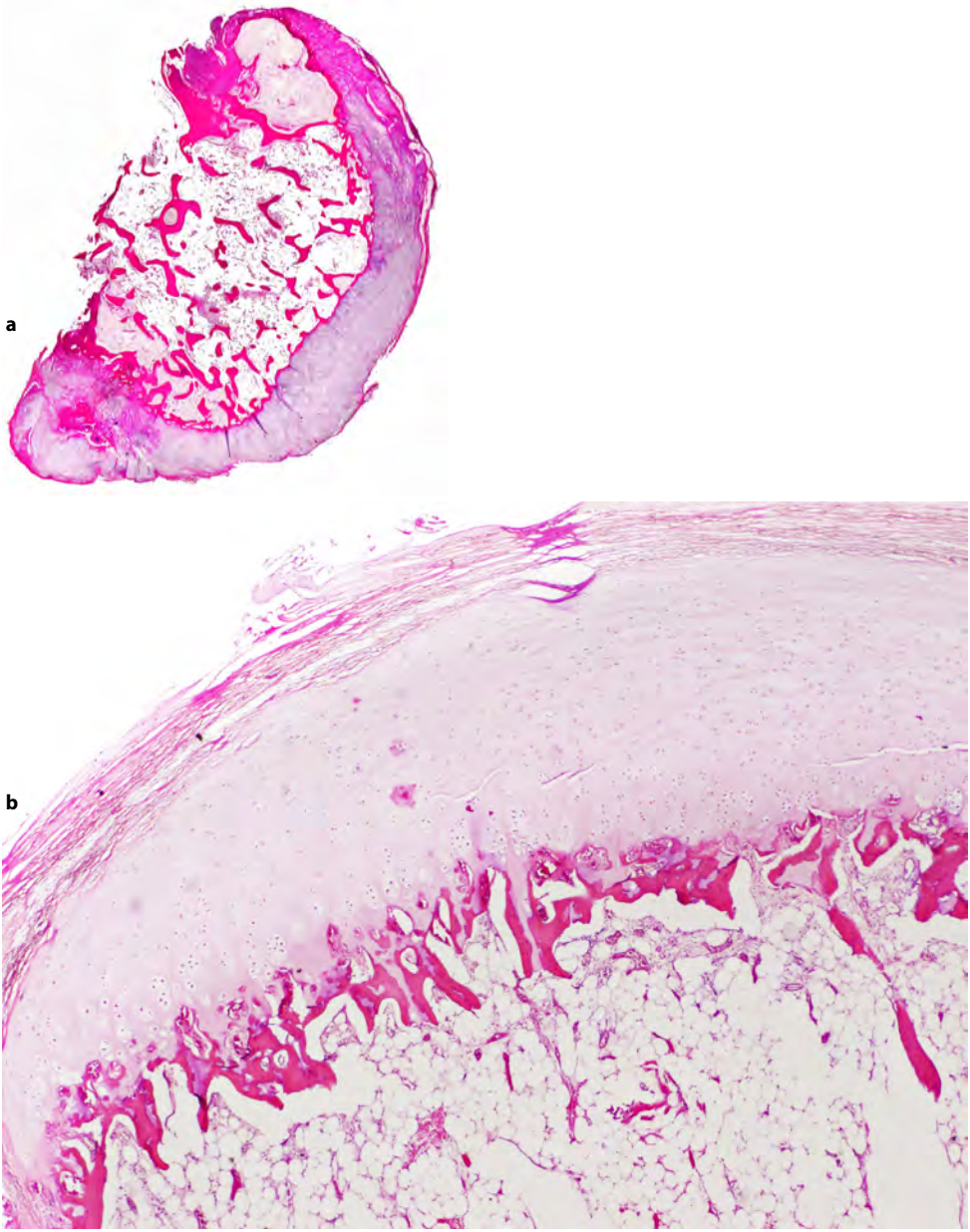


Figure 2 a, b. Histology: a) histotopogram of osteochondroma, b) osteochondroma, magnified 80x, HE. Courtesy of Professor Ctibor Povýšil, MD, DSc.

MCE is the result of a developmental disorder of the epiphyseal cartilage (see **Fig. 2 a, b**). The bone structure within the exostosis corresponds to spongiosis and directly transitions into spongiosis metaphysis. The compact of the exostosis also transitions smoothly into the compact of the long bone. The apex of the exostosis sometimes shows a structureless calcareous shadow, corresponding to a calcified cartilaginous cap. Exostoses and/or secondary deformities are usually observed by 12 years of age. Radiographs reveal exostoses on enlarged metaphyses, and exostoses increase in size with growth and migrate from the metaphyses to the diaphyses. Lesion growth slows during adolescence and no new lesions appear in adulthood. The localization of cartilaginous exostoses tends to be polyostotic, polytopic and not symmetrical. The radiographic picture is decisive for the diagnosis.

Left (top and bottom): two *exostoses of the right proximal* ***humerus*** – boy 13 years old – and two exostoses of the outer end of *the right clavicle* – girl 8 years old. **Bottom centre**: *Toes of right* ***foot*** – boy 9 years old: hypoplasia of *middle phalanges of 2nd–5th toes*, small exostoses on *distal phalanges of 1st, 3rd–5th toes*. *Left* ***hand and wrist*** – girl 9.5 years old: closed growth physis of the basal article of the 4th finger and growth physes of the 3rd–5th metacarpals, which are shortened. Extended metaphyses of the base and middle article of the 3rd finger and the middle article of the 4th finger, where small exostoses are visible. Ulna is distally shortened and pronounced, wrist articulation is between radius, os lunatum and naviculare. Exostoses between distal end of radius and ulna. **Middle top**: right ***hip joint*** – boy 13 years old: diffuse expansion of the proximal femur, wide valgus neck and flat epiphysis of the femoral head; exostoses around the greater and lesser trochanter, at the outer edge of the acetabulum and externally from the spina iliaca anterior superior. Slight protrusion of the acetabulum into the pelvis. **Right**: right ***knee*** – boy 9.5 years old: diffuse metaphyseal expansion, sessile and pedunculated exostoses, two eight splints applied with the aim of temporary medial hemi-epiphysiodesis and gradual correction of knee valgus.

Copies of radiographs from the archive of the Centre for Defects of Locomotor apparatus, Olšanská 7, 130 00 Praha 3 were used.

Radiographic features

Irregularly expanded metaphyses with sessile or pedunculated growths are observed, which are directed towards the diaphyses of long bones. The affected long bones are often shortened, sometimes showing tibiofibular or radioulnar synostosis (more often distal), which prevents supination and pronation of the forearm. The distal end of the ulna and the proximal end of the fibula may be shortened, widened or convoluted. A valgus deformity then develops at the knee and ankle joints. A clinodactyly or brachydactyly may develop on the fingers or toes. Exostoses also occur in the flat bones, more commonly along the crista ossis ilei and on the vertebral edge of the scapula, at the ends of the clavicles and on the ribs. They are rare on the vertebral bodies, sacrum and mandible, but do not occur on the skull vault.

Clinical symptoms usually appear in the first 10 years. In predilection localizations, multiple rigid growths are found, sometimes painful on palpation. The impaired growth of the long bones

leads to asymmetrical shortening and curvature of the long bones, to articular deformities with restricted range of motion. A common and typical ulnar and volar hand deformity is referred to as Madelung's deformity, caused by impaired growth of the distal end of the ulna by an osteochondroma (**Spranger** et al. 2018, **Marik** 2001). An analogous growth disorder sometimes occurs at the distal end of the fibula and leads to biomechanically severe valgus and instability of the upper ankle joint.

Mode of Inheritance is AD with 100% penetrance for males and lesser penetrance for females. The higher incidence and more severe manifestations of MCE are in males. There is considerable variability in the expression of disability within a family, with 1/3 of cases occurring sporadically. The average **incidence** is reported to be around 1 : 50,000 live births. However, the frequency of occurrence varies considerably.

Molecular basis and pathogenesis

Most cases of MCE are caused by mutations in the *EXT1* gene located on chromosome 8q24.11-q24.13 or the *EXT2* gene on chromosome 11p11-p12. These genes encode exostosin 1 and 2, transmembrane glycoproteins that catalyze the polymerization of heparan sulfate. Mutations result in loss of tumor suppression. Exostoses arise in heterozygotes after somatic mutation of the second, functional allele (loss of heterozygosity). Malignant degeneration of multiple exostoses is caused by mechanisms involving other genes. The most severe forms of disease and malignant transformation are associated with mutations in *EXT1*. A third gene causing MCE is located on chromosome 19p (Le Merrer et al., 1994, cited by **Spranger** et al., 2018).

Course and prognosis

The average height of men is 170 cm, women 155 cm (**Spranger** et al. 2018). Deformities, impaired joint range, centration and disproportionality of the long bones affect functional disability. In adulthood, exostoses no longer enlarge and new ones do not form. Exostoses can cause oppression of nerves (e.g. nervus peroneus communis), blood vessels, spinal roots and spinal cord, and rarely can cause urinary tract obstruction, intestinal obstruction or uterine malposition in pregnant women. Haemothorax has been described in a 12-year-old girl as a consequence of rib exostosis (**Taybi** and **Lachman** 1996). Sarcomatous degeneration is estimated by various authors to account for 2–10% of **MCE** cases. Rapidly growing, painful exostoses in adulthood are suspected. Most commonly in the hip region, proximal end of the humerus and in osteochondromas of the flat bones. Rarely, malignancy occurs before age 10 and after age 50. The radiographic sign of malignancy is loss of bone structure, blurred exostosis and dissolution of calcifications in the cartilaginous cap where chondrosarcoma develops. When malignancy is suspected, bone scintigraphy, CT, MRI, and ultrasound are indicated (**Matejovsky** et al. 1988). Life prognosis is good if malignancy does not occur. Dispensing of affected patients with regard to detection of precancerous changes is necessary throughout life. Detection of oncogenic markers in adulthood appears to be important (**Mařík** 2001). Early osteolytic changes can be detected by monitoring urinary markers of osteoresorption (**Mařík** et al. 2000).

Treatment

Surgical removal of exostoses is indicated in cases when exostoses cause pain, limitation of joint movement (the exostosis may grow into the joint space), the closure of adjacent bone, or oppression of nerves, blood vessels and other soft tissues around the exostosis. Exostoses suspected of malignancy must be removed immediately with the periosteum and cartilaginous cap. Affected individuals are dispensed as precancerous, and instructed on the need for self-examination. Madelung's deformity of the forearm can be addressed by corrective osteotomy of the radius and extension of the ulna (**Masada** et al. 1989). In the growing period of desaxation of the knee and ankle joints and unequal length of the lower limbs, we indicate epiphysiodesis for permanent (drilling) partial or complete. The timing of the procedure is discussed in collaboration with the anthropologist. For desaxations in the knees and ankles, we now prefer temporary hemi-epiphyseodesis using eight-plates. After growth has ceased, unequal length (and at the same time desaxation) can be addressed by lengthening the limb with an external fixator (**Marik** 2001) or corrective osteotomies. Bone remodelling during these procedures is very good (author's experience).

Differential diagnosis (**Taybi** and **Lachman** 1996, **Spranger** et al. 2018)

1. Enchondromatosis is characterized by enchondromas in the metacarpals (metatarsals) and phalanges of the hands (feet), with radiologic evidence of streaky lucencies in the metaphyses of the long bones. Exostoses are small and sporadic. Isolated exostoses are also found in cases of metachondromatosis. Maffuci syndrome presents with multiple hemangiomas in addition to multiple enchondromas and exochondromas. In both of these generalized chondromatoses, the percentage of malignancy is high, ranging from 30% to 50% (**Matejovsky** et al. 1988). Enchondromatosis localized to one limb or half of the body is referred to as Ollier's disease.

2. Solitary osteochondromas cannot be distinguished radiologically or histologically from multiple exostoses.

3. Exostoses may also develop in some other bone diseases and syndromes, e.g. trichorinophalangeal syndrome, type 2 (Langer-Giedion), Turner syndrome, brachydactyly type E and XYY. Co-occurrence of hypochondroplasia or achondroplasia and multiple exostoses has also been described. Exostoses have also been found in association with pseudohypoparathyroidism, morbus Legg-Calvé-Perthes, cardiopathy, and in association with mental retardation, schizophrenia, Wilms tumor, etc.

4. Isolated exostoses may result from mechanical irritation of the periosteum, subperiosteal posttraumatic hemorrhage or periostitis.

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METABOLICKY ZDRAVÁ OBEZITA: ZDRAVÁ TUKOVÁ TKÁŇ CHRÁNÍ PŘED METABOLICKÝMI PORUCHAMI

METABOLICALLY HEALTHY OBESITY: HEALTHY ADIPOSE TISSUE PROTECTS FROM METABOLIC DISORDERS

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SUMMARY

Obesity represents one of the biggest global threats to human health. Various diseases and metabolic disorders often accompany obesity making it one of the leading preventable causes of death worldwide. However, the development of metabolic disorders in obese patients also seems to be preventable. The metabolically healthy obesity (MHO) is a unique phenotype that allows the body to accumulate an excessive amount of lipid mass and maintain healthy metabolic functions. The metabolic health in MHO is not impaired mostly because the lipid mass is safely stored in adipose tissue (AT). AT is a connective tissue specialised in storing metabolic energy in the form of lipids. On the other hand, high concentration of lipids in non-adipose tissues can cause "lipotoxic" damage, which results in the development of various metabolic disorders including type 2 diabetes. AT of individuals with MHO has an exceptional lipid-storing ability and fully functional metabolism. Genetic factors largely determine the storing capacity of AT; however, the metabolic health of AT can be affected by dietary and lifestyle factors. Thus, the MHO phenotype could be partly induced in patients with unhealthy obesity. The understanding of cellular mechanisms behind MHO is critical in order to reduce the impact of obesity pandemic on the health system.

Keywords: obesity, metabolic health, adipose tissue, adipocyte, omega-3 fatty acids

INTRODUCTION – THE OBESITY PANDEMIC

The prevalence of obesity exceeds its all-time worldwide maximum every year. A study with almost 20 million participants from 200 different countries estimated that obesity prevalence has nearly tripled since 1975 [**27**]. Over 650 million adults were obese in 2016, which is around 13% of all adults worldwide. For the first time in the history of mankind there are more obese than undernourished people. Moreover, both these extremes can co-exist within the same country, even within the same community. In the past obesity was considered as the disease of the rich; however, obesity is no longer a problem of high-income countries, and some low-income countries considerably

contribute to the global obesity prevalence. Obesity is associated with a variety of metabolic disorders; therefore, the obesity pandemic represents a great burden for the health system and has tremendous economic consequences [**8**].

The primary cause of obesity is the imbalance between energy intake and energy expenditure. If energy intake chronically exceeds energy expenditure the body is forced to store the energy surplus. Adipose tissue (AT) is a connective tissue composed of adipocytes: cells specialised to store metabolic energy in the form of lipids, mostly triglycerides (TG). Obesity develops when an excessive amount of TG accumulates and forces AT to expand. AT expansion in obesity puts stress on the musculoskeletal system, which increases the risk for the development of diseases such as osteoarthritis [**2**]. However, AT expansion itself is a protective mechanism as it keeps lipids safely stored in adipocytes. The storage capacity of AT can be eventually exceeded resulting in ectopic lipid accumulation in the liver or skeletal muscle [**18, 29**]. The ectopic lipid accumulation decreases the sensitivity of non-adipose tissues to insulin and promotes the onset of various metabolic disorders.

Obese individuals display an increased incidence of the metabolic syndrome: a cluster of conditions contributing to the development of cardiovascular diseases and type 2 diabetes. These conditions include high blood pressure, increased plasmatic levels of glucose and lipids, and abundant fat accumulation in the abdominal area. The incidence of metabolic disorders in obesity largely depends on the body fat distribution. The expansion of visceral AT (abdominal obesity) is considered more detrimental due to its connection to the portal vein and visceral organs [**16**]. On the other hand, the expansion of subcutaneous AT (scAT) is not linked to the metabolic syndrome and it is considered protective [**37**]. Individuals with higher visceral AT expansion exhibit the apple-shaped body type, while scAT expansion (especially gluteofemoral scAT expansion) produce pear-shaped body type. Besides the body fat distribution, the metabolic functions of AT, particularly its ability to store lipids, play an important role in the protection against metabolic disorders.

Insulin resistance is another condition that often accompany obesity. Cells with decreased insulin sensitivity require more insulin to take up glucose from the bloodstream; therefore, pancreatic beta cells need to increase insulin secretion. Insulin resistance can eventually develop to type 2 diabetes if the endogenous insulin production is insufficient to promote cellular glucose uptake. The intramuscular TG accumulation is considered one of the main causes of insulin resistance [**19, 29**]. Another major cause of insulin resistance is a high plasmatic concentration of non-esterified fatty acids [**5**]. Both ectopic TG accumulation and high plasmatic fatty acid levels are results of insufficient lipid-storing ability of AT. The maintenance of proper AT functionality can therefore prevent from insulin resistance and the onset of type 2 diabetes.

Considerable part of obese individuals is protected against the development of metabolic disorders [**21, 22, 42**]. They represent the metabolically healthy obesity (MHO). The MHO phenotype is determined by both genetic and environmental factors. Genetics predestine the body fat distribution and the maximal storage capacity of AT. However, the functionality of metabolic processes in AT under the constant calorie overload can be affected by dietary and lifestyle factors.

The definition of MHO

The World Health Organization (WHO) defines obesity based on the body-mass index (BMI), which is calculated as a weight in kilograms divided by the square of height in meters (kg/m^2). According to WHO an obese individual has BMI greater than or equal to 30. WHO also defines obesity as "abnormal or excessive fat accumulation that may impair health". On the other hand, there is no unified definition of MHO, which makes it very challenging to determine the MHO prevalence [**33**]. In addition, MHO seems to be only a transient phenotype as individuals with MHO can eventually develop metabolic disorders [**3**]. MHO phenotype requires AT with healthy metabolic functions. The improvement of AT health status could slow down or even reverse the transition towards unhealthy obesity.

AT dysfunction in obesity

Excessive lipid accumulation causes AT to expand and remodel. AT remodelling changes properties of adipocytes and their metabolic functions. Pathological AT remodelling results in the impairment of AT metabolic functions, which subsequently manifest on the whole-body level. It was demonstrated that diet induced obesity in mice causes pathological remodelling of visceral AT depot with the main mechanisms being adipocyte hypertrophy and the induction of chronic inflammatory state [**39**].

Adipocyte hypertrophy is the enlargement of the adipocyte due to increased TG accumulation. Adipocyte hypertrophy is measured by the adipocyte volume, which is the ratio between lipid accumulation and lipid catabolism. High adipocyte volume seems to increase the risk for the development of type 2 diabetes [**44**]. AT can also expand by adipocyte hyperplasia, which is the formation of new adipocytes. It was proposed that in adult human the number of adipocytes is fixed and the adipocyte hypertrophy is therefore the predominant mechanism of AT expansion [**38**]. However, in this study only abdominal scAT was examined, while another study reported that in human gluteofemoral scAT the main AT expansion mechanism is hyperplasia [**40**]. These findings again support the advantages of the pear-shaped fat distribution as adipocyte hypertrophy is more adverse AT expansion mechanism than hyperplasia.

Adipocyte hypertrophy creates local hypoxic areas in AT. Hypertrophic adipocytes grow faster than the supportive vasculature that provides them with oxygen. Numerous studies documented poor AT oxygenation in obese individuals [**17**, **41**]. AT hypoxia contributes to the shift of the adipocyte secretion profile towards higher production of pro-inflammatory cytokines that activate immune response. Immune cells macrophages subsequently migrate into AT and further produce pro-inflammatory cytokines leading to vicious circle of inflammation. Macrophages in AT are also responsible for removing remnants of dead adipocytes as abundant adipocyte hypertrophy might eventually result in cell necrosis. Macrophages removing dead adipocytes form crown like structures, which are used as the marker of AT inflammation [**24**].

Pro-inflammatory cytokines produced by hypertrophic adipocytes and macrophages alter AT metabolic functions. Adipogenesis and lipogenesis: the formation of mature adipocytes and the synthesis of TG molecules in adipocytes respectively, decrease in AT of patients with type 2 diabetes

[**7**] and in adipocyte cultures treated by pro-inflammatory cytokines [**15, 35**]. Impaired ability to store lipids causes elevation in the levels of fatty acids first in the interstitial space in AT (between adipocytes) and later in the bloodstream. Non-esterified fatty acids are very reactive molecules, and they damage adipocytes and other cells by interfering with various signalling pathways and changing the composition of cellular membranes [**23**]. As mentioned above, high fatty acid levels and their lipotoxic effect decrease insulin sensitivity of non-adipose tissues as well as AT itself [**5**]. In addition, AT from obese individuals has lower production of adiponectin [**36**]. Adiponectin is a hormone secreted by adipocytes that stimulates lipid catabolism and has strong insulin-sensitising effects [**11, 45**].

In conclusion, dysfunctional AT in obesity is characterised by a high degree of adipocyte hypertrophy, chronic inflammatory state, altered adipocyte secretion profile, and impaired AT metabolic functions (**Figure 1**). Hypertrophic adipocytes cause AT hypoxia as their cellular mass grow faster than blood vessels that provide them with oxygen. Hypertrophic adipocytes also produce less insulin-sensitizing hormone adiponectin and more pro-inflammatory cytokines, which attract macrophages into AT and augment AT inflammation. Pro-inflammatory cytokines impair basic metabolic functions of adipocytes including lipid storing, which further worsen the metabolic health of AT and other organs.

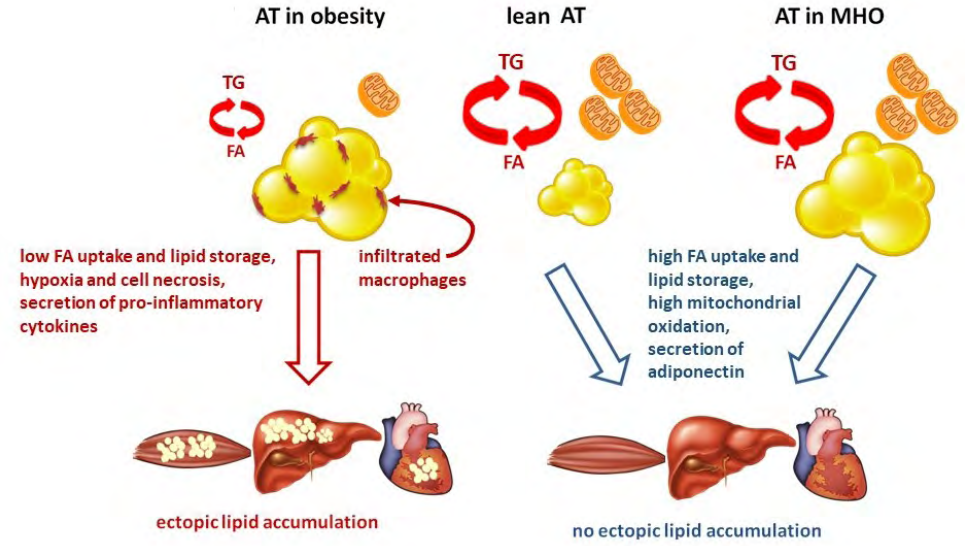

Figure 1. AT in unhealthy obesity is in chronic inflammatory state that is characterised by the infiltration of macrophages and it exhibits an impairment of basic metabolic functions that subsequently damages other organs. AT in MHO is fully functional and resembles AT of lean individuals. AT: adipose tissue; FA: fatty acids; MHO: metabolically healthy obesity; TG: triglycerides.

The improvement of AT health in obesity

As a state of chronic overconsumption obesity is characterised by constantly elevated plasmatic nutrient levels. AT has a key role in controlling plasmatic levels of fatty acids and glucose. The nutrient-buffering function of AT is particularly important for the maintenance of MHO phenotype.

Futile cycle based on triglyceride lipolysis and fatty acid re-esterification (TG/FA cycling) is a metabolic process in AT that greatly contributes to the control of systemic lipid homeostasis [**12, 32**] (**Figure 2**). TG/FA cycling is also linked with de novo lipogenesis (DNL), which is a process of fatty acid synthesis from non-lipid precursors such as glucose. High rate of DNL can therefore greatly affect plasmatic glucose levels. Moreover, TG/FA cycling has high energy requirements and it increases fatty acid oxidation in adipocytes to produce more ATP [**31**]. One of the markers of healthy AT is a high rate of mitochondrial fatty acid oxidation and a high expression of mitochondrial metabolic genes seems to be associated with MHO [**25**]. AT with high activity of TG/FA cycling is able to flexibly direct the flow of fatty acids towards oxidation or storage within adipocytes. Such ability represents one of the main features of healthy AT.

The activity of TG/FA cycling as well as the rate of lipid catabolism are supressed by obesity in both rodents and humans [**4, 34**]. In addition, hypertrophic adipocytes have reduced ability of lipogenesis and lipid storage, which causes ectopic lipid accumulation and insulin resistance. A class of insulin-sensitising drugs known as thiazolidinediones (TZD) was developed to promote lipogenesis in AT [**6**]. By promoting lipogenesis TZD stimulate AT expansion and lead to increased weight gain [**30**];

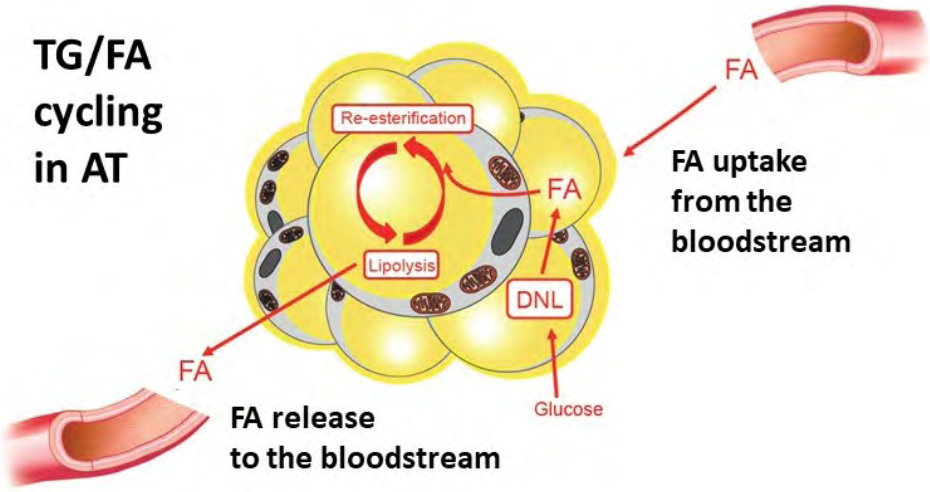

Figure 2. TG/FA cycling in AT contributes to the maintenance of the whole-body lipid homeostasis by regulating plasmatic levels of fatty acids. AT: adipose tissue; DNL: de novo lipogenesis; FA: fatty acids; TG: triglycerides.

however, they seem to improve metabolic functions of AT including the stimulation of TG/FA cycling. TZD were reported to have various side effects; therefore, pioglitazone is the only TZD remaining in clinical use, while safer "second-generation" TZD are currently tested in clinical trials [**14, 43**].

Other compounds with a potent ability to improve metabolic functions of AT are n-3 polyunsaturated fatty acids (omega-3). Omega-3 can be found in dietary sources such as flaxseeds and walnuts; however, omega-3 from marine sources like marine fish, krill and marine plankton seem to be more efficient in the modulation of AT functions. Omega-3 were reported to increase the rate of TG/FA cycling in adipocytes and other cell types [**4, 20**], stimulate lipid catabolism in AT [**9**], reduce AT inflammation [**1**], and even increase the levels of hormone adiponectin [**10**]. It was further demonstrated that omega-3 together with TZD exerted synergistic beneficial effects on the improvement of metabolic health of obese mice, with the combination of omega-3 and the second-generation TZD MSDC-0602K having the strongest effect [**4**].

Results of these studies suggest that the metabolic health of AT in obesity can be effectively improved by TZD and by including omega-3 of marine origin in the diet. Besides dietary interventions, the risk for the development of metabolic disorders in obesity can be greatly reduced by continuous reduction of AT mass. The most efficient way to achieve that is to shift the energy balance towards energy expenditure by lowering calorie intake and increasing physical activity.

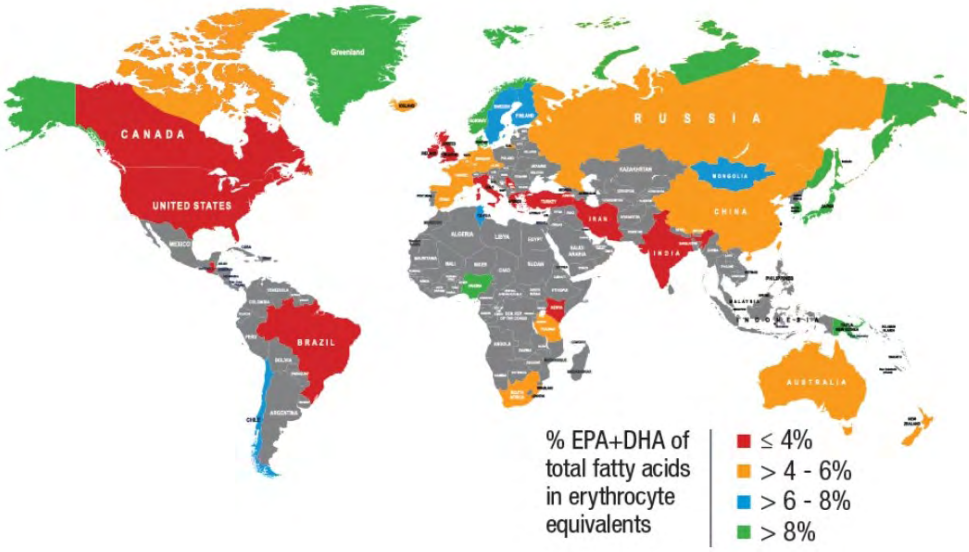

Figure 3. Adapted from - www.grassrootshealth.net/project/dactionomega3. The visualization of omega-3 (EPA and DHA) consumption in different countries by omega-3 index. Omega-3 index determines omega-3 content on cellular membranes of red blood cells and its values correlate with the incidence of various diseases. DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid.

CONCLUSION – METABOLIC HEALTH FOR PEOPLE OF ALL SIZES?

The MHO phenotype requires AT that is able to maintain its proper biological functions even under extreme conditions of calorie overload. Genetic factors play an important role in the maintenance of metabolic health in obesity. The ethnicity was shown to have a great effect on the fat distribution, which determines the type of AT expansion, propensity to adipocyte hypertrophy and hyperplasia and the maximal AT storage capacity. A study with more than 16 000 participants found higher prevalence of abdominal obesity in White Americans compared to Black and Hispanic Americans [**28**]. Another study comparing 5 different ethnic groups found the highest risk of cardiovascular disease in South-East Asians followed by Caucasians and the lowest amount of visceral AT in African Caribbean Black group [**26**].

Metabolic functions of AT, on the other hand, can be affected by diet. An omega-3 index is a parameter that reflects omega-3 intake in diet by calculating omega-3 content on the membranes of red blood cells (**Figure 3**). It was suggested that omega-3 index could be used as one of the determinants of metabolic health as low omega-3 index is associated with a high incidence of cardiovascular diseases and possibly also Alzheimer´s disease, cancer and other diseases [**13**]. As mentioned above, beneficial effects of omega-3 on AT functions have been demonstrated in numerous studies. Including sufficient omega-3 intake in the diet therefore seems to be an efficient way to improve metabolic health of AT.

Healthy AT is necessary for the maintenance of MHO phenotype mostly because of its ability to protect the rest of the body from the lipotoxic damage by storing lipid excess in adipocytes. The health status and functionality of AT are equally important parameters as the total AT mass. All of these parameters should be taken into account in order to maintain metabolic health in obese individuals.

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GEOTERMÁLNÍ VODA POUŽÍVANÁ PŘI LÉČEBNÉ REHABILITACI. VODNÍ ZDROJE V POLSKU PRO PACIENTY S PORUCHAMI POHYBOVÉHO APARÁTU. ZNALOSTI PRO FYZIOTERAPEUTY

GEOTHERMAL WATER USED IN MEDICAL REHABILITATION. WATER RESOURCES IN POLAND FOR PATIENTS WITH LOCOMOTOR SYSTEM DISORDERS. KNOWLEDGE FOR PHYSIOTHERAPISTS

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SUMMARY

The period of human life can be divided into three phases. If there are not any symptoms of primary pathology, a rapid development, proper shaping and growing is observed in newborns, infants, children and adolescents. Anabolic processes prevail.

The early adult life – from 20 to 50 years of age – is a phase of full activity, good health, with predominance of anabolic processes.

From around the age of 50, a period of slow domination of catabolic, regressive, processes begins, leading to dysfunctions and diseases. The suffering of older people is caused by diseases and dys-

functions of the spine, hips, knees, feet and shoulders. These processes can be slowed down or even inhibited by the appropriate rehabilitation. The best conditions for therapeutic rehabilitation are in geothermal waters. In the article we inform where there are Geothermal Rehabilitation Centers in Poland and where geothermal waters are potentially easy to obtain. The use of these waters is a task for the Polish population, doctors, physiotherapists, the Polish Geothermal Association and of the Polish Government.

Key words: orthopaedics, neurology, disorders, deformations, illnesses, physiotherapy using geothermal water.

INTRODUCTION

From the beginning of human history, there have been and there are incorrect developments, disorders, diseases, pain syndromes, trauma of movement apparatus and other forms of motor disability. Medical help for suffering people was constantly needed. In antiquity – there were medics [Latin "medicus" – doctor] and barbers – later surgeons. From 1741 – after the publication of the book: *L'Orthopédie ou l'art de prévenir et de corriger dans les enfants, les difformités du corps le tout par des moyens à la porté des pères & des mères & de toutes les personnes qui ont des enfants à élever* by Prof. Andry Nicolas, royal physician from Paris – the word "orthopaedics" became known. The word "orthopaedics" comes from two Greek words – orthos – straight, correct and pais – child. Rehabilitation and physiotherapy as parts of medicine are derived from orthopaedics over the next centuries.

Already in antiquity, the warmth of water was valued as a treatment. Emperor Agrippa first used the term "therms" (Latin "thermae") for pools in which health was recovered in warm waters. Nowadays we can say – they were "geothermal baths" or "medical gymnastics in geothermal water". In Poland prof. Julian Sokolowski and prof. Jacek Zimny were the first scientists speaking about using of geothermal water also in medical therapy (**Fig. 1a, 1b, 3, 7, 8, Tab. 1**).

Soaking in geothermal, mineral water is good for the mind, body and soul. Here are some reasons why it feels so good. Is good for our skin, while our bodies are covered in a protective shield that's also porous. Skin absorbs what surrounds it, the good and the bad. The waters contain minerals that can detoxify and can help remedy skin ailments. So soaking can be beneficial to your skin. Skin will feel fresh, clean, and be aglow. The second role is the heat. The warmth of hot water can help alleviate pain sensations. Science has shown that soaking in hot water blocks pain receptors in bones and muscles. Next is the good vibes. While it's tempting to drift into a serene solitude while soaking in geothermal warm water, it's also a great place to connect with others. People gather in the warmth to visit, catch up, share and collaborate. And we all know how important it can be to our wellbeing to stay connected to others. Then relaxation and the clarity. Soaking in warm water can be deeply restorative. It can help reduce stress, bring a sense of peace and serenity. And by combining a warm soak with a cooling experience like our cold plunge, you're upping your chances of a great night's sleep. The heat of our water combined with minerals helps release nasal and lung congestion in powerful ways. You'll emerge breathing clearly and deeply. Spending quality time in warm waters is good for us, on the inside and the out.

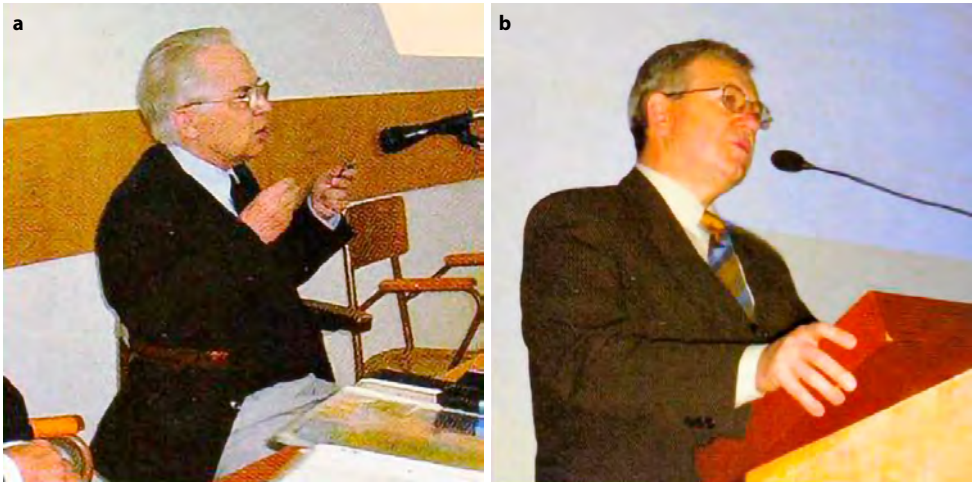

Fig. 1a, 1b. Prof. Julian Sokołowski (1932–2004) (Fig. 1a) – initiator and creator of „Polish Geotherms". Prof. Jacek Zimny (Fig. 1b) – professor at Akademia Górniczo – Hutnicza (Polish) / University of Technical Science (English) – continuator of „Polish Geotherms Program".

Fig. 2a, 2b. Prof. Wiktor Dega (Poznań) (fig. 2a) had spoken – in physiotherapy important knowledge and sensible heart. Prof. Stanisław Piątkowski (Lublin) (fig 2b) had spoken – good rehabilitation doctor only after successful study of orthopedics.

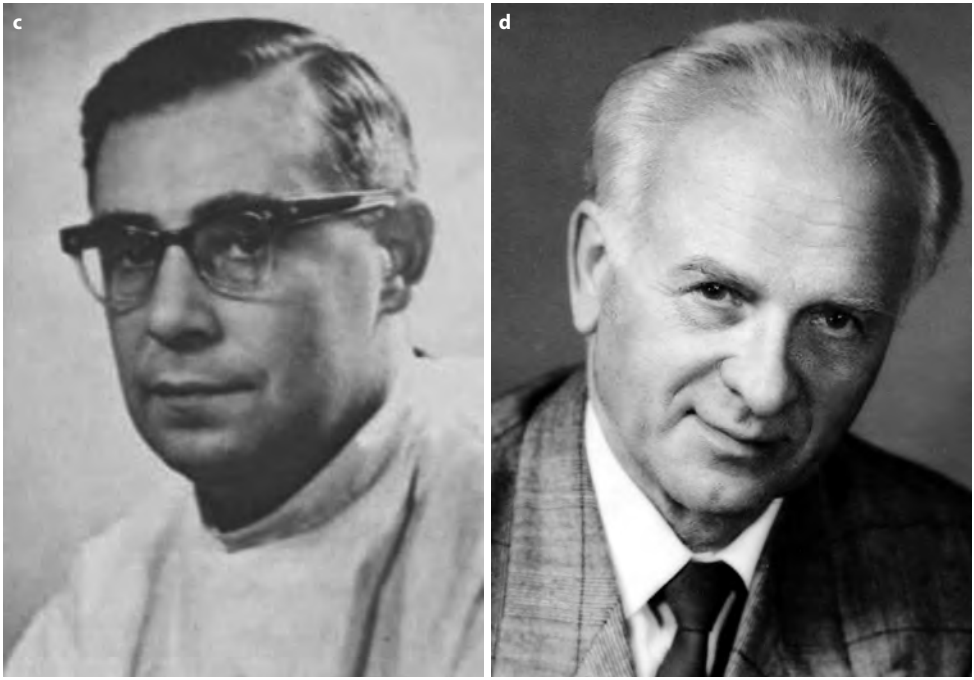

Fig. 2c, 2d. Prof. Józef Kamiński (Lublin) (fig. 2c) had spoken – good results in therapy if the doctor is fully educated in orthopedics. Prof. Ignacy Wośko (Lublin) (fig. 2d) had spoken – of a no good doctor if not properly educated and even more worse if „overeducated".

CAUSES OF PATHOLOGY

Causes of pathology – of developmental disorders in children and pain syndromes in adults. In orthopaedic and rehabilitation literature as well as in medical practice, it is most often assumed that the pathology of the musculoskeletal system is associated with "muscle weakness" and "strengthening" is recommended as a treatment. This concept is probably adopted from sport – where strong muscles mean better results in jumping, running or other disciplines. But that does not happen in medicine. The pathology of the musculoskeletal system in children and adults is associated mostly with limitations in the range of movement of the joints and incorrect positions of parts of the body. These disorders are the result of shortening of muscles, tendons, fascia and joint capsules – symptoms typical for the Syndrome of Contractures and Deformities [SofCD] according to Prof. Hans Mau (**52**) and Lublin observations from the years 1973–2021 (**25, 28**). We observed also other groups of patients with – shortening of muscles, tendons, fascias, capsules – and there are cases with symptoms of Minimal Brain Dysfunction [MBD]. In these neurological abnormalities we observed sub-spasticity of the muscles and very often laxity of joints as a result of "unprofitable biochemical changes of the collagen". In cases of MBD there are deformities in children and pain syndromes in

adults. Shortenings in orthopaedics are called "contractures" (Latin contractura / plural – contracturae). It is a concept presented by the Poznań and Lublin orthopaedic team since 1960s–70s – by prof. Wiktor Dega, prof. Stanisław Piątkowski, prof. Ignacy Wośko, prof. Józef Kamiński **(Fig. 2a, 2b, 2c, 2d)** – but also by professors of orthopaedics abroad – Prof. Jørgen Reimers (Denmark), Prof. Harald Thom, Prof. Hans Mau, Prof. Hans Zwipp, Prof. Britta Fuchs (Germany). Prof. Viktor Bialik (Israel), Prof. Tibor Vizkelety, Prof. Kalman Szepesi, Prof. Janos Rigo (Hungary), Prof. Ivo Marik (Czech Republic), Prof. Mikhail Dudin (Russia), Dr. Piet van Loon (Netherlands) and many others.

Necrosis of the femoral head in children – known as Perthes' disease, is also associated with MBD. In MBD there are not only changes in the anatomy and function of the musculoskeletal system (References **23, 26, 27, 29, 31, 38, 39, 40, 41, 59**), but also appears in many children some as psychological changes. Children with MBD mostly are restless, anxious and nervous and like to jump. Repeated jumping on a hard surface for weeks and months leads to fractures of the trabeculae of the femoral head – this starts the process of Perthes disease. The illness can last over 3–5 years. This process we described in 2021 in an article: Perthes disease. Etiology. Symptoms. Physiotherapy. In the International Journal of Orthopaedics Research, USA / Kansas, 2021, Pages 1–7 (**48**).

In all cases with symptoms of Minimal Brain Dysfunction [MBD], with all contractures of joints, with all symptoms of "incorrect position of parts of the body" – the best therapy is stretching exercises in geothermal water. Such therapy can cure all contractures, correct posture of all parts of the body and improve function.

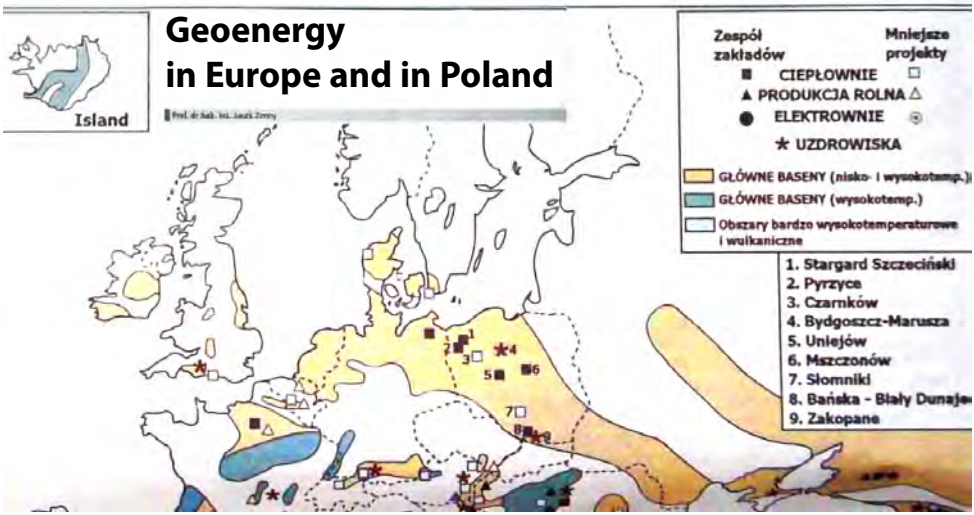

Fig. 3. Publication by Prof. Jacek Zimny of an article about the „Energy of geothermal water in Europe and in Poland". Big resources of geothermal water – chance for the Development of many Rehabilitation Centers in Poland.

MATERIAL

The group of patients, which is described in this study, includes many hundreds of patients treated by the authors – T. Karski since 1961, M. Domagała since 1979, J. Karski since 1989 and K. Karska since 2010. The conclusions contained in this study are also based on observations concerning the effectiveness of treatment in geothermal water in Hungary, because in the years 1961–2000 suffering people were directed to Hungarian Geothermal Rehabilitation Centres. At that time, the knowledge of prof. Karoly Papp, prof. Kalman Szepesi and prof. Janos Rigo from the University Orthopaedic Department in Debrecen had for us a very important value. Thanks to the activity of prof. Karoly Papp – geothermal water lead directly to the building of Houses for the Orthopedic Department, to make it easier for rehabilitation exercises in Hospital (personally observation by T. Karski in the years 1968–1978).

CHILDREN AND ADOLESCENTS – REVIEW OF DISEASE

Already in newborns and infants, disturbances in anatomy and function of joint, as well as development and growth may occur. These disorders – as mentioned earlier – had been described by Prof.

Fig. 4. Szaflary in Podhale – south region of Poland. Rehabilitation exercises in geothermal waters are especially profitable in locomotors system disorders. Photo T. Karski (2019).

Fig. 5. Bukowina Tatrzańska – mountain region of Poland. Rehabilitation exercises in geothermal waters give the best results in the therapy of locomotors system disorders. Photo T. Karski (2009)

Hans Mau (Tübingen) called these anomalies in German "Siebenersyndrom" – in English "Syndrome of Seven Contracture". It is a pathology concerning the anatomy, positioning of individual parts of the body and the range of joint mobility. In Lublin, the pathology and the resulting disorders – in form of deformities, insufficiency in function we called "Syndrome of Contracture" (SofC) since 1973 – after T. Karski's scholarship in a program of DAAD at the University Orthopaedic Department in Heidelberg and in Essen and J. Karski – after a scholarship at the Orthopaedic Department in Heidelberg in 1995. In 2006 in Lublin – the eighth pathology related to shank varus deformity was added to the "Seven Contracture Syndrome" (T. Karski and J. Karski). Since then, from 2006, in Lublin this syndrome we called "Syndrome of Contracture and Deformation" (SofCD). This, described in 2006 pathology – if not treated or treated ineffectively, can lead to a deformity called "Blount's disease" (References **26, 27, 28, 29, 33, 34, 38, 39, 40, 41, 42, 43**).

Another group of pathologies in the form of deformation in children and pain syndromes in adults – are resulting from a pathological function of the Central Nervous System [CNS]. This pathology is known as Minimal Brain Dysfunction [MBD]. The MBD arises mostly as a result of asphyxia in the foetal or perinatal period (References **26, 29, 31, 39, 41, 42, 44**). These early pathologies require early treatment – and such therapy we can see as "prophylaxis for adult people".

Thus – according to the authors – two groups of primary pathologies' are in children about 30% – 40% and the same percent – of diseases and pain syndromes in adults. There are, of course, other causes of pathologies of the musculoskeletal system which require differential diagnosis and special treatment methods.

Here we present some pathologies of the musculoskeletal system – in children, adolescents and adults, requiring treatment, preferably through stretching exercises in geothermal water.

A. Hip dysplasia – this pathology may have a different aetiology:

a) may be one of the symptoms of the Syndrome of Contracture and Deformation (SofCD),
b) may be associated with laxity – it is a neurological factor of MBD associated with pre- or perinatal asphyxia,
c) may be due to spasticity or sub-spasticity of the hip adductors – it is also a neurological factor of MBD.

A common feature of hip dysplasia is contracture (shortening) of the hip adductors, sometimes joint instability (**12, 13, 22, 23, 24, 27, 29, 31, 39, 40, 43**). Treatment consists in overcoming contracture of the hip adductors, which becomes easier in geothermal waters (**20**). Abduction nursing is neces-

Fig. 6. Chochołów / Witów – mountain region of Poland. Rehabilitation Center. Exercises in geothermal water – best form in the therapy of locomotors system disorders. Standing on the right leg – arrow – causes of scoliosis. Photo T. Karski (2016)

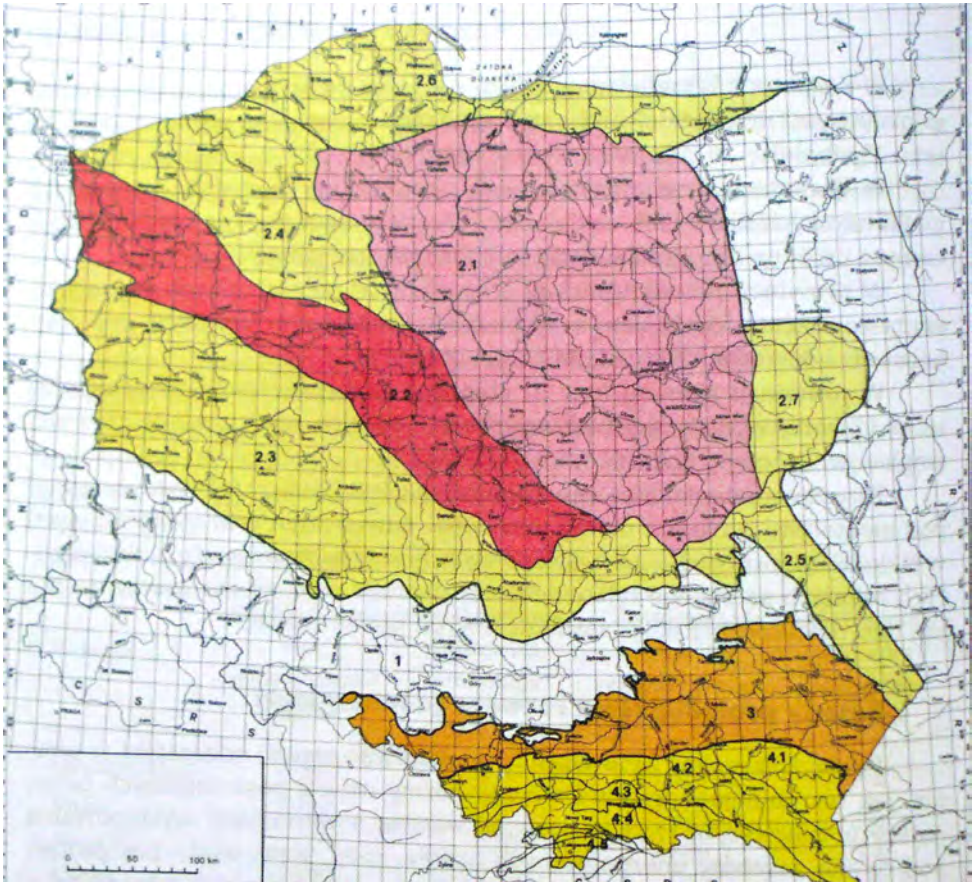

Fig. 7. Map of Poland. Coloured fields – geothermal waters in Poland. White fields – geothermal area not recognized. Prepared by: R. Ney, J. Sokołowski. J. Zimny. Geothermal Rehabilitation Centers – the future for Poland.

sary from birth to the end of the first year of life, sometimes longer. Recovering from hip abduction after being carried by mother or father is faster, more effective and pleasing to the baby in geothermal waters. Due to its influence on the circulatory blood system, warm water effectively protects the hip against possible complications – such as aseptic necrosis of the femoral head. Such treatment is particularly important in children with primary symptoms of MBD. Please note – carrying babies facing to the front, without hip abduction – is a mistake, unfortunately common practice currently in many countries in Europe .

B. Torticollis – this pathology may have the following causes:

a) may be a symptom of Contracture and Deformation Syndrome,

b) may be the result of a traumatic delivery,
c) may be congenital as a torticollis cum tumor neonatorum.

The treatment consists in overcoming the contracture of the muscle sternocleidomastoid by stretching – rotation therapy – by twisting the child's head towards the torticollis (!). This rotation stretching has been used in Lublin since 1974 and many years of observations confirm that this method is fully effective. This method of therapy was published in many articles – in 1991 in Orthopädische Praxis in Germany (Reference **5, 13**) and in 2015 in the American Research Journal of Medicine and Surgery. Also, in the following years, in other journals in the USA, England and in the Czech Republic (Reference **28, 29, 33, 39, 40, 41, 54, 58, 59**). Here we want to underline that only "the rotation by stretching to the torticollis side" is fully optimal therapy. In our opinion, the effectiveness of the treatment of torticollis in geothermal waters by rotation stretching is much faster and more effective. Using this method in physiotherapy brings beneficial effects not only in new-borns and infants, but also in 3–4 year old children. However, good cooperation between the physiotherapist and the parents is necessary.

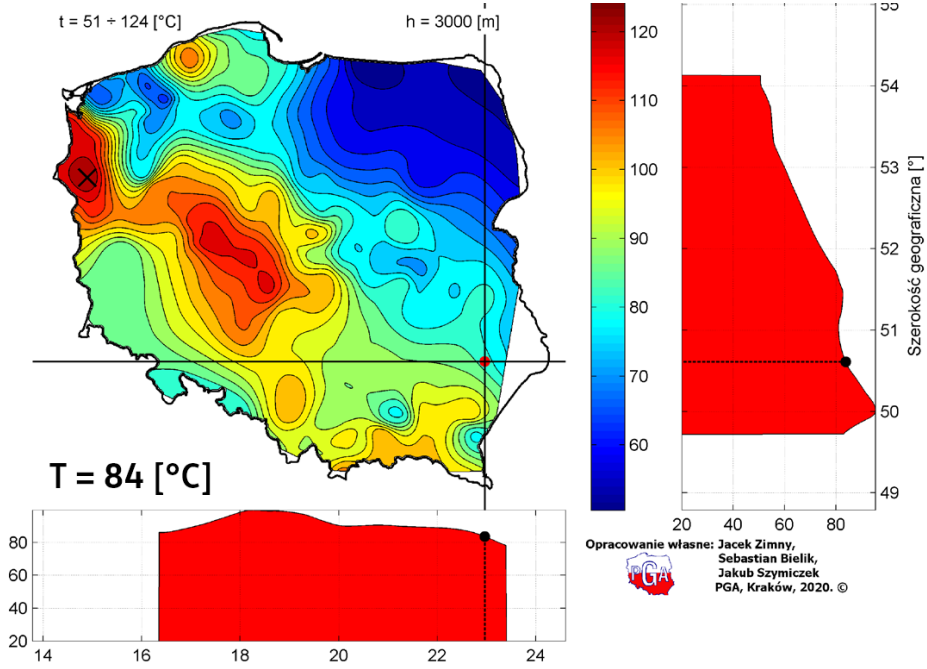

Fig. 8. Zwierzyniec – town in the southern part of Lublin District. Geothermal waters to a depth of 3000 m with a temperature of water 84 °C. The map was prepared by Prof. J. Zimny and his team.

Location Zwierzyniec Roztocze	Borehole depth [m] Prepared by J. Zimny, K. Szczotka, M. Strus	Temperature of water [°C] Prepared by J. Zimny, K. Szczotka, M. Strus
Roztocze Zwierzyniec	500	28
	1000	39
	1500	50
	2000	61
	2500	72
	3000	84
	3500	95
	4000	106
	4500	117
	5000	128

Tab. 1. Geothermal Water in Zwierzyniec. Beneficial depth of 3000–3500 m.

C. Foot deformities. Valgus, flat-valgus deformities of the feet are most often the result of shortening of the triceps muscles (Latin M. triceps surae [MTS]) and Achilles tendons in cases of MBD. Such pathology affects approximately 13% of children in Poland (References **4, 5, 6 ,7, 8, 9, 10, 11, 14, 16, 17, 18, 38, 39, 40, 41, 42, 43**). The most common causes of MBD are, as mentioned before, the asphyxia of the foetus during pregnancy or delivery. Treatment is based on stretching, that is elongation of the Achilles tendons and the musculus triceps surae. Treatment in geothermal waters is the most effective.

D. The so-called idiopathic scoliosis. For over two thousand years, the aetiology / causes of these spinal deformities were unknown. Observations made in Lublin (1984–2007, and particularly 1995–2007) indicate that scoliosis are a result of the impact of biomechanical factors in the situation of primary asymmetry of movements and positioning of the hip joints and the pelvis itself. In children with scoliosis, restriction of adduction in the extension position of the joint is found in the right hip. A loss of internal rotation of this joint is often also present. Sometimes there are flexion contractures in both hips, as a symptom of MBD, causing an anterior tilt of the pelvis which makes development of spine deformity easier.

Hip movement asymmetry is a part of the symptoms, Syndrome of Contracture and Deformation (Prof. H. Mau and Lublin observations) (**35, 38,39, 40, 41, 42, 43**).

In the development of scoliosis plays two biomechanical factors – a) permanent standing "at ease" on the right leg and b) walking. Standing – because the right hip is more stable and standing is easy and safe. Walking – because fully limited movement of the right hip is forced to make walking compensatory movements of the pelvis and spine – leading to rotation deformity and stiffness of the spine.

The aim of the therapy – is to receive full movement of the right hip, proper position of the pelvis and full movement of the spine. Stretching exercises are the only proper therapy of scoliosis – and these preferably – in sport and in geothermal water. Only the flexion and rotation exercises are the correct form of therapy. Prof. Stefan Malawski (Warsaw, Otwock) was the first in Poland to approach this issue. It is necessary to point out that sports such as karate, aikido, taekwondo, tai chi, kung-fu, yoga, which involve elements of stretching are an excellent method of causal prophylaxis and therapy of scoliosis.

ADULTS – REVIEW OF DISEASES

In adults, the problem is pain, most often in the spine, hips, knees and shoulders.

A. Spine. In adults and rarely in adolescents – "back pain syndromes", other descriptions: "discopathy", "lumbar spine stenosis", "lumbar disc hernia" are really caused by:

a) lumbar hiperlordosis – due to hip flexion contracture in persons with MBD,
b) due to degenerative scoliosis in type – "S" 1st etio – patho – genetic group / type (epg) – starting already in childhood as "C" or "S" type in 2nd A/B epg group,
c) due to the stiffness of the spine – this is a specific type of "I" scoliosis in the 3rd epg group in the Lublin classification (this type of scoliosis was described in 2004 – T. Karski),
d) spondylolisthesis,
e) congenital defects of the spine and / or chest,
f) other, rare genetic causes or disease syndromes.
g) the rapid cooling of the peri – spinal soft tissues during intense work or sport (observation from 2018 – T. Karski).

Neurosurgeons recommend mostly surgical treatment in the case of back pain, usually diagnosing "prolapsed nucleus pulpous". The authors' experience says (**19, 21, 25, 26, 27, 28, 29, 32, 34, 38, 40, 41, 42, 43, 44, 55**) that surgical treatment does not bring the expected results and only physiotherapy proves to be important and effective. These observations were also confirmed in scientific discussions by T. Karski with Prof. K. F. Schlegel – (Head of the Orthopaedics Department in Essen, Germany – T. Karski in scholarship programs of DAAD was in Essen's Orthopedic Department in 1973) – during meetings at Orthopaedic Congresses in the years 1975–1980. Our recommendations (Reference **38, 43, 44, 45**) for the patients with "Back pain" are: physical methods of therapy: "chair extension" and exercises in geothermal water. Over the many years of observations we could confirm that kinesio-therapy in mineralised warm waters is easy to do and very effective. Contractures in the area of the hips, pelvis and spine are easier to overcome in geothermal waters. Fully, no restricted function of the spine – means life without pain. As previously underlined, geothermal waters have a great analgesic effect. After rehabilitation exercises in geothermal waters good health conditions as well as "positive mental thinking" – return faster.

B. Hip. The hip joint in adults is often the site of pathology. The authors refer to the initial stages of the disease as "imperfect hips" (References **2, 15, 40, 41**). The advanced disease is "hip arthrosis". Left hip arthrosis is usually the result of dysplasia, which has not fully healed in childhood. Right hip arthrosis – this is very often the result of permanent standing 'at ease' on the right leg. This pathological phenomenon occurs in the "Right Leg 'at ease' Standing Syndrome". This syndrome is a medical observation from 1997, when the aetiology of the so-called idiopathic scoliosis was described (1995–2007, T. Karski). There are numerous publications of ours about "Right Leg Standing Syndrome", mostly in the USA (References **22, 30, 31**). In the "Imperfect Hip Syndrome" and particularly in "hip arthrosis" the symptoms include – loss of the full range of movements, anatomical changes of the femoral head or both femoral heads, and even their necrosis process and, as a result – pain, difficulty walking, limping and disability. According to many authors, the loss of mobility of the hip joint alone, as "only this one symptom" can lead to hip pathology. These observations made in Lublin (T. Karski, J. Karski) is also recognised by many foreign authors, including professor Britta Fuchs from the Medical University of Idstein, professor Hans Zwipp from the Orthopaedics Department in Dresden (Germany) (**30, 31, 34, 35, 38, 39, 40, 41, 42, 43, 55**). Treatment should primarily include recovery of abduction, internal rotation, and extension of the hip or both hips. Geothermal water stretching exercises are the best and most effective.

C. Knee. Knee problems in adults are associated with primary axis disorders – persisted from childhood – varus of shanks or valgus of the knees in older children, youth and adults. Both defects make pain and difficulties in walking – because of instability of the knee joint. Another cause of pathology is knee contracture – even small 3–5 degrees. A large group of patients have problems with the patellofemoral joint, when the patella is in its lateral position; there is a subluxation of the patella, symptoms of chondromalacia and patello-femoral arthrosis.

A large group of patients have knee problems associated with incorrect sitting. It is a common pathology, but its recognition and descriptions come only from the years 2012–2021 (T. Karski, J. Karski, M. Domagała) (References **35, 37, 38, 46**). Treatment of knee pain syndromes is very effective and beneficial when performed in geothermal waters. Many years of observations confirm that in warm water, exercises to improve knee stabilisation, to remove the pain – are a pleasant and effective form of therapy.

D. Feet. There are many diseases, deformations leading to foot dysfunction and pain syndromes (References **4, 5, 6, 8, 9, 10, 11, 12, 13, 14, 35, 36, 37, 38, 47, 49, 53, 55**) and we present a list of "feet problems":

1. Pes plano-valgus,
2. Hallux valgus,
3. Foot insufficiency and foot pain in neuro-muscular dysfunction (MBD),
4. Chronic rotational distortion syndrome of the talocrural joint (References **35, 36, 37, 38, 3–36, 47, 52**)
5. Morton's pain syndrome (References **47, 52**),
6. Köhler II disease (References **47–52**),

7. Pathology resulting from the loss of plantar flexion of the toes. In the diagnosis of this dysfunction, the flexion test of the toes is important (References **4, 5, 6, 8,9, 10, 11, 12, 13, 14, 16, 17, 18, 55**).

The radiating pains to the shank and the foot – can appear in degenerative scoliosis and lumbar hiperlordosis. Here – we underline – the differential diagnosis in "foot pain syndrome" – is necessary.

All the above – described deformities and foot dysfunctions can be successfully treated by exercises in geothermal waters. Rehabilitation in warm, mineralised water in order to regain stabilisation and increase the range of motion of the foot joints, plays an important role in improving the foot functions and at the same time has an effective analgesic effect.

E. Shoulder. Shoulder dysfunction is a common disorder for many people. The cause of pain syndromes – bearing various names, such as "painful shoulder contracture", "frozen shoulder" or "pain syndrome in the acromial region" – is known and described in many orthopaedic publications. Two main reasons are important in shoulder pathology according to our observations.

The first group of causes is pathology related to professional work performed "above the shoulder joint level" – e.g. car mechanic, housework – washing windows, stacking shelves, working in shops, warehouses, etc.

The second group of causes is related to overload and ischemia of the attachments of the muscles of the shoulder region and also often of the neck while working, when the muscles of the shoulder and neck are in constant isometric contraction – without any movement of the joint. This leads to ischemia and sometimes local minimal necrosis of the attachment of the muscle or certain regions of the muscle itself, and these symptoms are referred to as "enthesopathy". Very often, when the persons are working on a computer – the shoulder and neck muscles – m. trapesius, m. deltoideus, m. subscapularis, m. supraspinatus, m. infraspinatus – are in "contraction" and can appear ischemia in some parts of the tendons or muscles which triggers pain. Pain, makes the movement impossible. This results in a "shoulder contracture", referred to in situations of maximum pathology as "frozen shoulder". Treatment of shoulder pain syndromes is to improve circulation, regain movement, and the most effective way is exercises in geothermal waters. The therapy of "shoulder problems" especially "frozen shoulder" can take sometimes many years. In the past, patients were sent to geothermal waters in Hungary, now such therapy can be implemented in Poland.

BENEFICIAL PROPERTIES OF GEOTHERMAL WATERS

The beneficial effects of geothermal waters in physiotherapy are based on three essential elements:

1. warm water with a temperature of 36 or 38 degrees is an excellent analgesic in pain syndromes, and at the same time an essential anaesthetic,

2. water provides – according to Archimedes' law – buoyancy, offering the perfect possibility of kinesiotherapy.
3. minerals (**Fig. 4**) in geothermal waters are an important element for tissue reconstruction, for all anabolic, nutritional and regenerative as well as energy processes important in our every day activity, in physical work and in sport.

TREATMENT FOR DISORDERS OF THE MUSCULOSKELETAL SYSTEM IN GEOTHERMAL WATERS, ESPECIALLY FOR OLDER PERSONS.

Spine – recovery of flexion and extension movements, left and right deviations, as well as left and right rotation as the basic task. Recovering these movements in geothermal waters is easier, faster and more effective.

Hip – recovering abduction, internal rotation, and extension are essential tasks for every older person as a prophylaxis against arthrosis of the hip. The best results are obtained if the exercises are performed in geothermal waters.

Knee – Exercises in geothermal waters to improve the stability of the knee or to remove its flexion contracture are easy, more effective, pleasant and painless. As mentioned above, geothermal waters have an analgesic effect.

Foot – two areas of the foot require kinesiotherapy in geothermal waters – talocrural joint to recover dorsiflexion of the foot and plantar flexion of the toes. Only full and painless movements of the foot in the talocrural joints and flexion of the toes, ensure a painless and efficient locomotive function.

Shoulder – shoulder dysfunction and pain syndromes are the complaints of many middle – aged and elderly people. The therapy must be persistent for a long time and should achieve two goals. The first goal is to make the movements painless – and this is possible in geothermal waters. The second goal is to regain full abduction movement, external rotation as well as shoulder extension. Recovery through exercises such as "pendulum exercises" (Latin "manus pendula") with the limb pointing downwards (hanging) in geothermal waters is faster and more effective.

GEOTHERMAL WATERS IN POLAND

Location – information on where to build new rehabilitation centers with the use of geothermal waters (**Fig. 3, 4, 5, 6, 7, 8, Tab. 1**).

The authors (T. Karski, J. Karski, M. Domagała, K. Karska) know from their own medical observations many Geothermal Centers in Hungary, Slovakia and in Poland. A cooperation with the AGH (Polish:

Akademia Górniczo – Hutnicza) – (English: University of Science and Technology [UST]) from Kraków started in 1995 and it was a cooperation with Prof. J. Sokołowski until 2004 and currently with Prof. J. Zimny and his team (References **55–59**) **(Fig. 1**).

We known personally the Geothermal Rehabilitation Centers in the Tatra Mountain District – a district south of Poland in Białka Tatrzańska, Bukowina Tatrzańska, Szaflary and Chochołów **(Fig. 4, 5, 6).** Now the aim of our cooperation is to organize new Geothermal Rehabilitation Centres in other parts of Poland for example in the Roztocze Region (Zwierzyniec District). According to literature, Poland is the country to have the largest area of geothermal waters "under its surface". Professor Julian Sokołowski (1932–2004) – the Father of Polish Geotherms – during many Scientific Conferences and Sessions used to say "there is another Baltic with warm water under the Polish soil". The temperature of geothermal waters depends on the borehole depth and appropriate values are presented for the village of Zwierzyniec in Roztocze (**Table 1, Fig. 9, 10, 11, 12, 13, 14**). Polish geothermal waters have full mineral resources important for every human organism for its functioning, health and fitness. As an example, the mineral composition of Białka Tatrzańska in Podhale is provided (**Fig. 4**).

DISCUSSION

Benefits of termal water is well documented. Kecskés inform about situation in Hungary. Owe to the favourable geological circumstances Hungary is, in both thermal and medicinal waters, a rich area of the world. The medicinal waters based spas, with the joined (medicinal) treatments play important part in the health protection and in the process of cure and recovery (**51**). Many authors confirm benefits of thermal water in different aspects in prophylaxis and rehabilitation of moving apparatus (**1, 3, 50, 55, 56, 57**). In this article authors confirm benefits in patients requires different, special treatment. We speak about the young patients affected by disorders of growth and destroyed development and older patients suffering because of "pain syndromes". In orthopaedics and rehabilitation knowledge persist the opinion that "muscle strengthening exercises" are the best solution in the therapy. The opinion of general doctors, proclaim that analgesic drugs alone will relieve pain and insufficiency of movement apparatus in suffering people.

The authors of this publication claim that pathology, including pain syndromes, is usually associated with deficiencies in joint movement, faulty positions of the body parts, faulty loading and overstress during work or sports. Mostly these pathological symptoms are connected with shortening of soft tissues – fascias, tendons, muscles, capsules – and only stretching exercises are proper in the therapy. All these "shortenings" we call in orthopaedics "contractures". In therapy of "contractures" the best are stretching exercises – and the profitable exercises are in geothermal water. Also some kind of sport has the stretching elements. In this group is karate, aikido, taekwondo, or yoga. But in our opinion the stretching exercises in geothermal waters are "the best under discussion".

There are geothermal waters under the Polish soil – they only need to be brought to the surface and used, not only for industrial purposes, for heating houses, schools, offices, hospitals, factories,

public institutions, electricity production, but also for rehabilitation therapy and prophylaxis. This can happen through the development of Geothermal Rehabilitation Centres for Polish citizens and for patients from other countries of Europe.

CONCLUSIONS

1. Pathology of the musculoskeletal system in the form of deformities in children and adolescents and pain syndromes in adults are very common – 15% of children and 30% of adults.
2. The most common locations of pain are the spine, hips, knees, feet and shoulders.
3. The causes of pathology are connected mostly with loss of movement in joints – called "contractures of joints", with instability of joints, overstress in professional activity, in sports and in everyday domestic work.
4. The primary cause are pathologies described as "Syndrome Contracture and Deformities" (Prof. Hans Mau) and "Syndrome of "Minimal Brain Dysfunction" (MBD). Both Syndromes are connected with problems during pregnancy and the delivery period of a child's life.
5. Treatment of children and adolescents, according to the authors, is the recovery of movements through beneficial forms of sport, such as karate, taekwondo, aikido, yoga, and through kinesiotherapy in geothermal waters.
6. Treatment of adults is to remove pain, regain motor activity and full function of the joints, preferably through stretching exercises in geothermal water.
7. Application of therapy using geothermal water, requires prior differential diagnosis – orthopedic, neurological, pediatric or internal. Only the correct diagnosis enables the implementation of the correct therapy.
8. There are already numerous Geothermal Rehabilitation Centres in Poland. The next ones will be created in a coordination program of "collective cooperation" of doctors, physiotherapists, local governments, Central Authorities and Scientific Teams of the Polish Geothermal Association.

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HYPOFOSFATEMICKÁ KŘIVICE: PŘEHLED A PŘÍPAD STRESOVÉ ZLOMENINY U 30,5LETÉHO PACIENTA LÉČENÉHO OD DĚTSTVÍ KONVENČNÍ LÉČBOU

HYPOPHOSPHATEMIC RICKETS: A REVIEW AND A CASE OF STRESS FRACTURE IN A 30.5-YEAR-OLD PATIENT ON CONVENTIONAL TREATMENT SINCE CHILDHOOD

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SUMMARY

The article summarizes the latest findings in terms of diagnosis, genetics, etiopathogenesis, pathobiomechanics, treatment, and demonstrate conventional treatment (including surgical management of lower limb deformities) in a patient with XLH from 7 years of age to adulthood when pseudo-fractures of the lower limbs occurred as a consequence of persistently impaired bone metabolism. Based on the experience of many years of follow-up and conventional treatment of 29 Czech patients with XLH (20 women, 9 men), the authors point out the difficulties characteristic of growing children (deformities progress in relation to growth) and adult patients (pseudofractures of the lower limbs, hyperostosis of the lumbar spine, delayed healing of fractures and corrective osteotomies, dental abnormalities, etc.) and discuss the benefits and risks of conventional treatment, the most serious of which are nephrocalcinosis and hyperparathyroidism. Last but not least, the authors point out the convincing results of prospective causal treatment not only children with with burosumab (Crysvita), a recombinant human IgG1 monoclonal antibody against FGF23, which have already been validated in double-blind studies, e.g. more patients experienced healing of fractures and pseudofractures compared to the placebo group.

Keywords: stress/fatigue fractures, hypophosphatemic rickets, X-liked hypophosphataemia, clinical findings, radiological features, pathobiomechanics, conventional therapy, human monoclonal antibody IgG1/Burosumab-twza against FGF23

INTRODUCTION

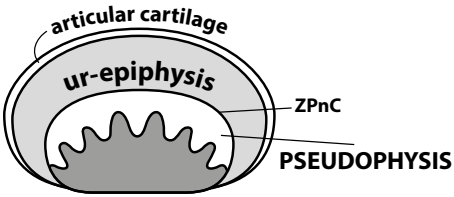
In 1937, Fuller Albright (**1**) noted that not all children with rickets responded favourably to treatment with high doses of vitamin D and calcium and that excessive hyperphosphaturia was present in these patients. He theorized about a rare hereditary form of rickets that differs from most cases of dietary deficiency rickets. Meanwhile, several subtypes of vitamin D-resistant rickets (VDRR) have been discovered, with X chromosome-linked hypophosphatemic rickets (XLH) being the most common cause of inherited phosphate wasting.

Hypophosphatemic rickets is a rare, genetically determined disease classified in the 26th group of Genetic skeletal disorders (**38**). In contrast to rickets caused by vitamin D deficiency, hypophosphatemic rickets is characterized by hyperphosphaturia, hypophosphatemia and normal serum levels of calcium (**12, 14**). The basic features of the X linked hypophosphatemia (XLH) are rickets, osteomalacia, odontomalacia and disproportinate short stature (**24**). Rickets represents disturbed mineralization and disorganization of the growth epiphysis (cartilage) during the growth period, when biomechanically severe skeletal deformities develop. Osteomalacia is the lack of mineralization of the trabecular and compact bone after growth has ceased. XLH is clinically manifested in the first years of life by deformities of the bones of the lower limbs, disproportional habitus, insufficient mineralization of bones and bone pain and dental abnormalities. In adults, bone and joint pain, osteomalacia, enthesopathy, early osteoarthritis, pseudofractures and spinal stenosis are encountered (**51, 14, 4**). The phenotypic features and severity of XLH vary from patient to patient. XLH is a metaphyseal bone dysplasia with typically disrupted endochondral ossification (**40**) – **Figure 1a**, **b, c**. The zone of provisional calcification in the growth plates is decalcified and thus enlarged.

Molecular basis and pathogenesis of hereditary rickets is heterogeneous (**38, 51**). This group of diseases is caused by mutations in various genes involved in regulating renal phosphate reabsorption (*PHEX*, *FGF23*, *DMP1*, *ENPP1, SLC34A3, CYP27B1, CYP2R1, CLCN5, FAM20C*) (**45, 51, 38**). The X-linked form is most common and that is why our study is focused on XLH.

XLH inheritance is dominant, which means that the gene responsible for the genetic disorder is located on the X chromosome and only one copy of the allele inherited from the parent who has the disorder is needed to cause the disorder. In this case, the X chromosome is associated with full penetrance of hypophosphatemia. Girls are twice as likely to be affected as boys, but only a proportion of female heterozygotes develop full VDRR syndrome. Skeletal involvement tends to be milder than in male hemizygotes. The disease manifests in all daughters of the affected male, all sons are healthy. If a woman with XLH has children with a male without the disease, their children, both male, and female will have a 50% chance of developing the disease. It means that 1/2 sons and 1/2 daughters will be affected. If both parents have XLH, then all of their female children will have XLH. Their male children will have a 50% chance of inheriting the disease-causing mutation from the mother and developing XLH. But around 20–30% XLH cases are due to spontaneous mutations (**46, 30**).

The **incidence of XLH** (MIM no. 307800) is 3.9 per 100,000 live births and a prevalence ranging from 1.7 per 100,000 children to 4.8 per 100,000 persons (children and adults) (**2**).



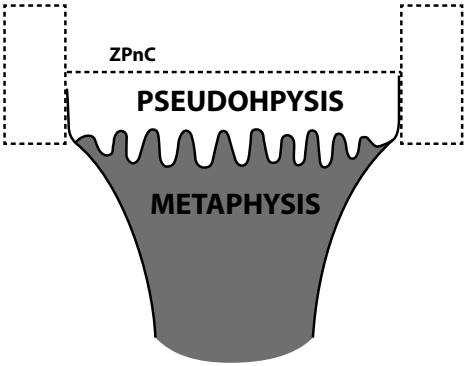
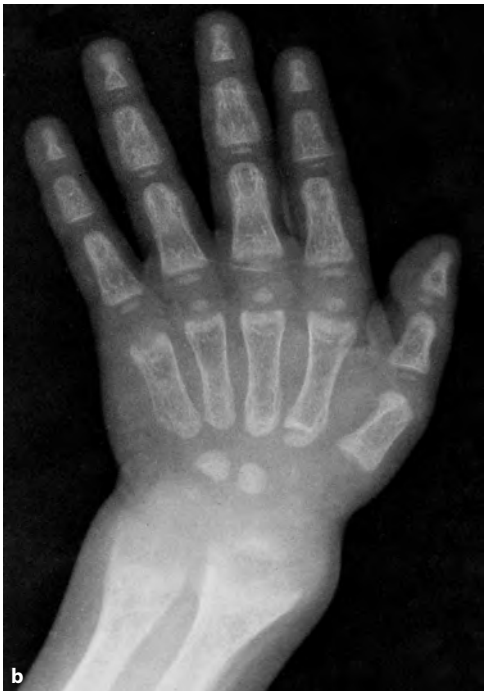
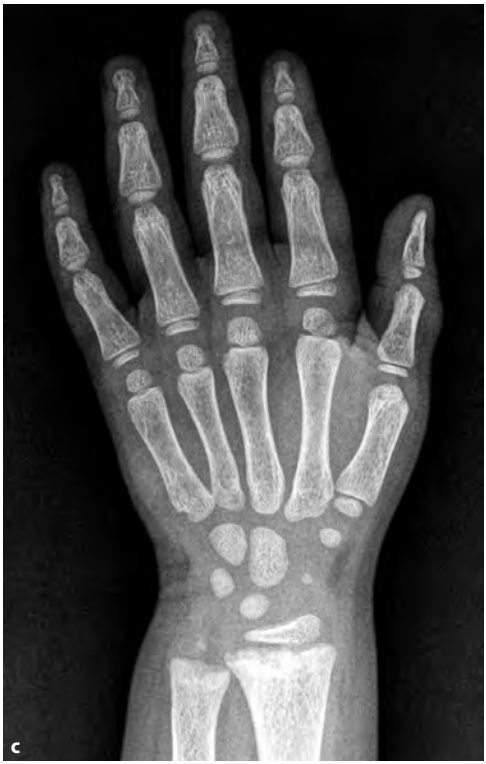


Figure 1 a. Schema of disrupted endochondral ossification of metacarpal bone according to Alan Oestreich, 2004. The zone of provisional calcification (ZPnC) in the growth plates is decalcified and therefore enlarged; ur-epiphysis symbolizes growing cartilaginous cells that have not differentiated into the shape and function of the epiphyseal plate.
Figure 1 b. X-ray of left hand, 2 years old boy – vitamin D deficiency rickets.
Figure 1 c. X-ray of the left hand, 6 years girl – hypophosphatemic rickets.
Both images show cup-shaped enlargement and fraying of the metaphyses in the wrist. Bone age is delayed.

a





Etiopathogenesis

XLH is associated with a mutation in the *PHEX* (Phosphate Regulating Endopeptidase Homolog, X-Linked) gene sequence that is located on the chromosome X at location Xp22.2-p22.1 (**48**). Approximately 350 different mutations have been identified in the PHEX gene by 2019 (**4**). Dysfunction of the PHEX protein caused by mutation leads to increased production of fibroblast growth factor 23 (FGF23) by osteocytes and odontoblasts by an unknown mechanism (**26**). Increased level of FGF23 inhibits renal phosphate reabsorption and cause renal phosphate depletion and low blood phosphorus levels (**4**). The failure of phosphate reabsorption in the proximal tubule of the kidney and the conversion of 25(OH)D to 1,25(OH)2D explains most of the clinical and radiological symptoms (**13**).

New research shows that FGF23-related pathways may also influence skeletal development in a phosphate-independent manner (**4**), with hypophosphatemia disrupting growth plate processes. Apoptosis of hypertrophic chondrocytes is arrested and chondrocyte proliferation is reduced. As a result, the organization of proliferating columns is lost (**59**). Hypomineralization of the newly formed bone leads to osteoid accumulation and bone weakening. When pressure is applied to the affected bones, they bend under pressure, and the load appears to affect the function of the hypomineralized growth plates, which together cause leg length to be affected more than arm span in XLH patients (**4**). The consequence of above is delayed ossification in the growth cartilage leading to growth failure, altered bone structure, reduced skeletal strength and the development of characteristic progressive skeletal deformities during the growth period and problems with bone mineralisation throughout the patient's life (**30**).

Main clinical findings (**23, 13, 51**) Most children with XLH have growth disturbances, short disproportionate stature, bowed legs (at 2 to 3 years of age), dolichocephaly, a waddling gait due to poor positioning of the large leg joints (varus femoral necks cause insufficiency of m. gluteus medius), a protuberant abdomen, delayed tooth growth and enamel hypoplasia, kyphoscoliosis, bone and tooth pain. Patients do not suffer from tetany and cramps, unlike patients with rickets from vitamin D deficiency (**46**). In adults, permanent problems or complications such as joint pain, muscle weakness, impaired mobility, tooth abscesses, hearing loss, hyperparathyroidism, osteomalacia, enthesopathy and ectopic ossification at tendon attachment sites, ossification of the posterior longitudinal ligament of the spine (it can cause canal stenosis and myelopathy), early osteoarthritis, pseudofractures and osteosclerosis, especially in the axial skeleton, occur (**51, 14**). Intellectual development is not impaired. Craniosynostosis should be suspected in the presence of signs of intracranial hypertension (**4**). Adult height ranges from 130–160 cm (**53, 44**).

Main radiographic features (30, 40, 51)

Typical are mild to moderate rachitic metaphyseal changes – see **Figure 2a–e.**

Wide growth epiphysis, metaphyseal cupping, fraying and flaring; bowing and tubular shape of the long bones; sparse trabecular bone structure and thinner fibrous cortical bone; Looser zones and

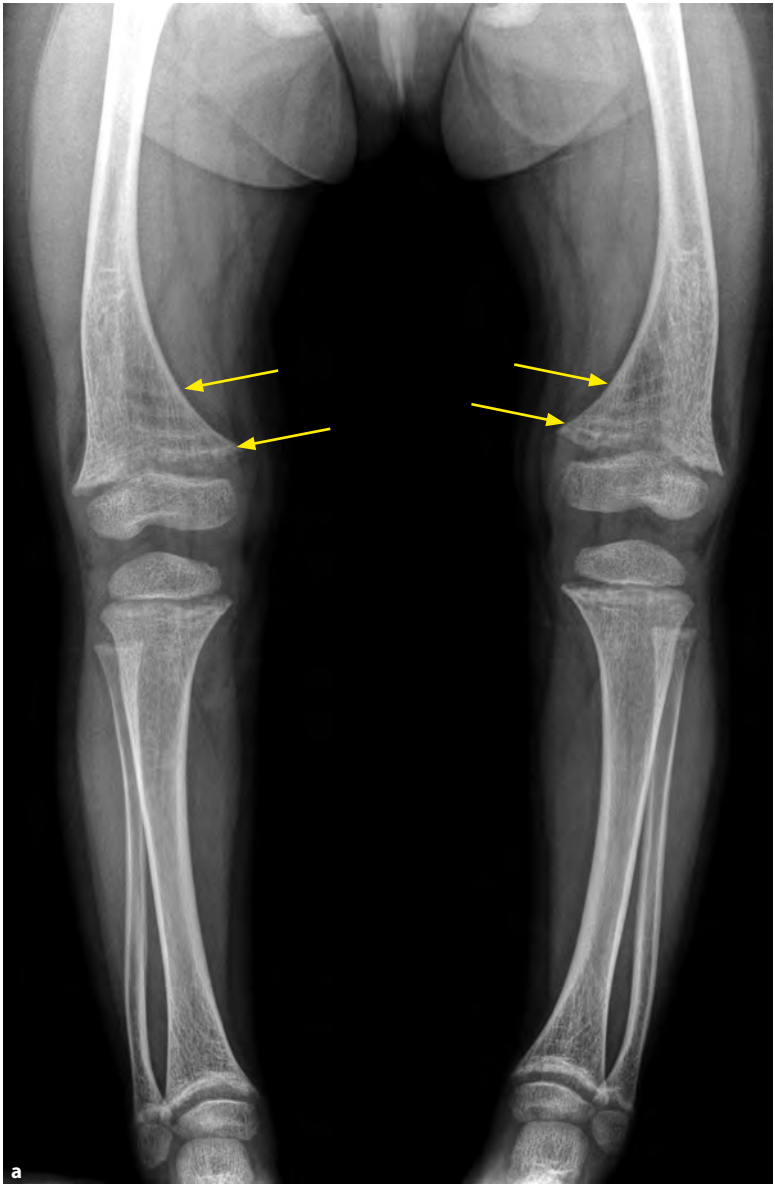


Figure 2 a–i. X-rays of children with XLH. See the wide growth epiphyses, cup-shaped enlargement and fraying of the metaphyses; the bowing and tubular shape of the long bones; the thinner fibrous cortical bone; the coarse and somewhat sclerotic bone trabeculae and transverse strips of increased bone density, the so-called Harris lines – see arrows in the distal metaphysis of the femurs. **a.** 4 years – anterolateral varosity of the distal femurs and mild proximal tibiae

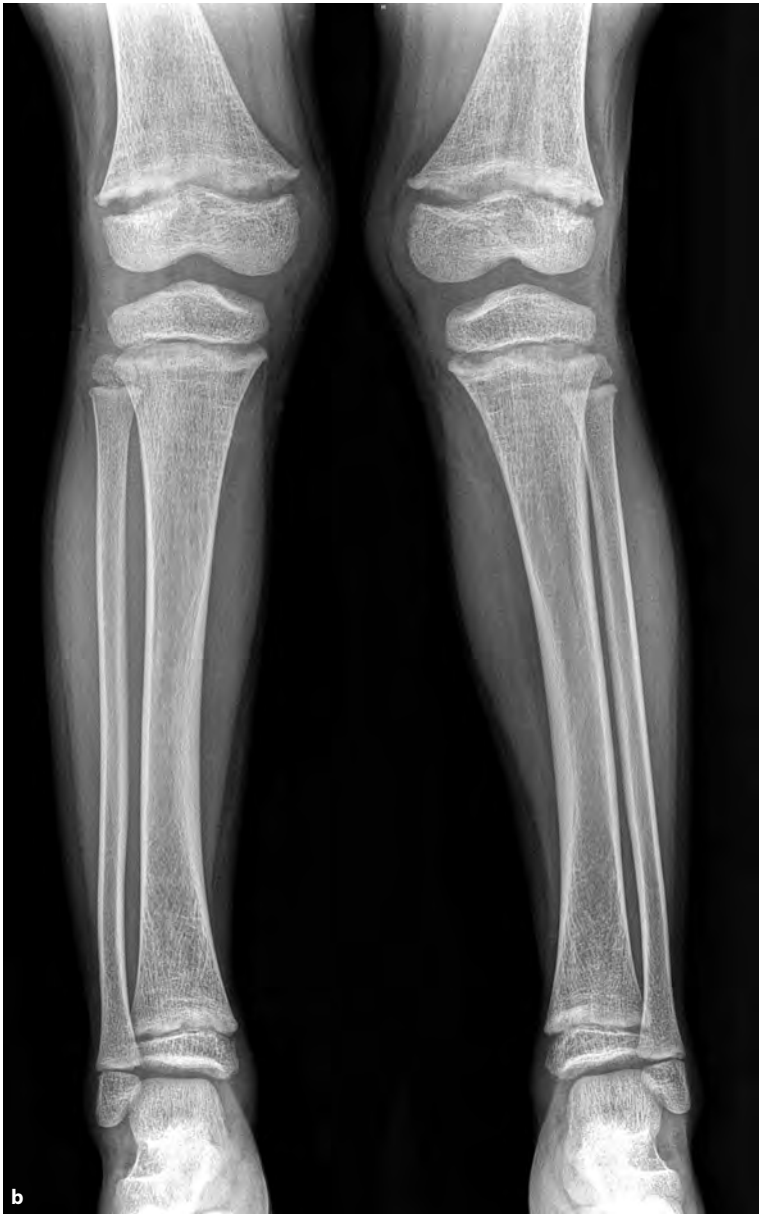


Figure 2 a–i. X-rays of children with XLH. See the wide growth epiphyses, cup-shaped enlargement and fraying of the metaphyses; the bowing and tubular shape of the long bones; the thinner fibrous cortical bone; the coarse and somewhat sclerotic bone trabeculae. **b.** 7 years – genua valga

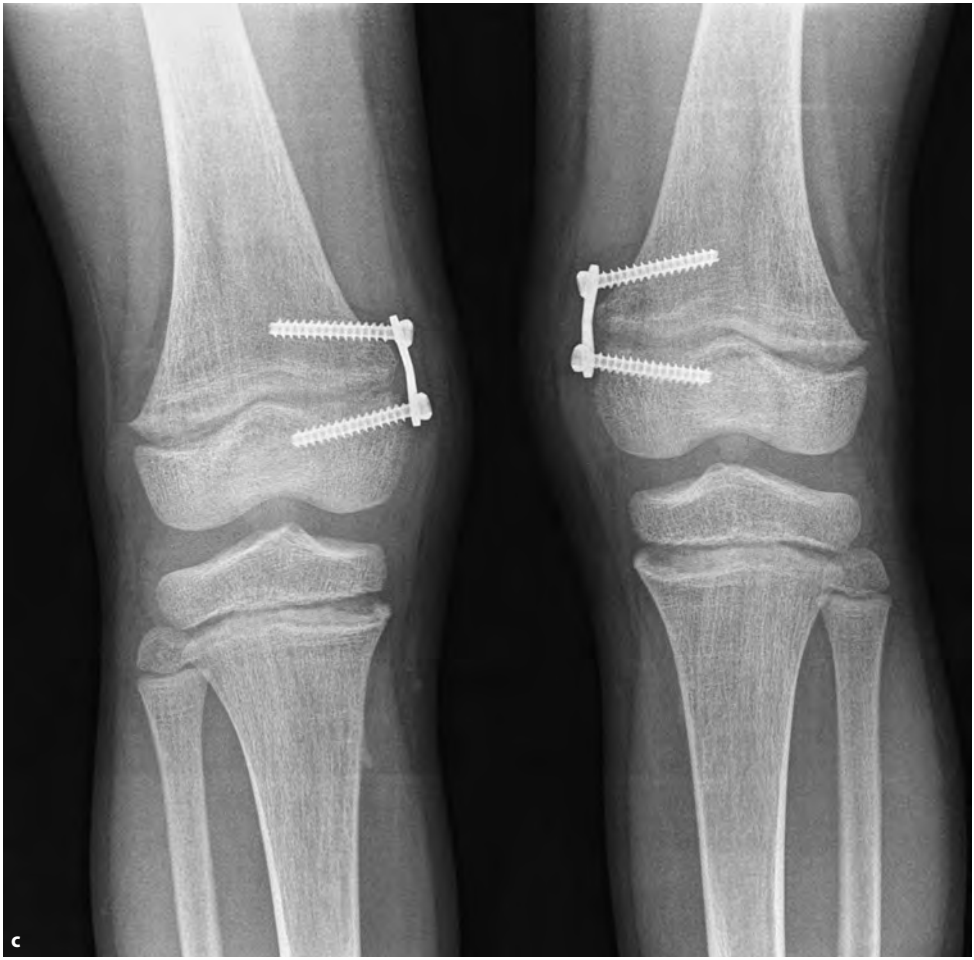


Figure 2 a–i. X-rays of children with XLH. See the wide growth epiphyses, cup-shaped enlargement and fraying of the metaphyses; the bowing and tubular shape of the long bones; the thinner fibrous cortical bone; the coarse and somewhat sclerotic bone trabeculae. **c.** 8 years – 12 months after distal medial femoral hemi-epiphysiodesis

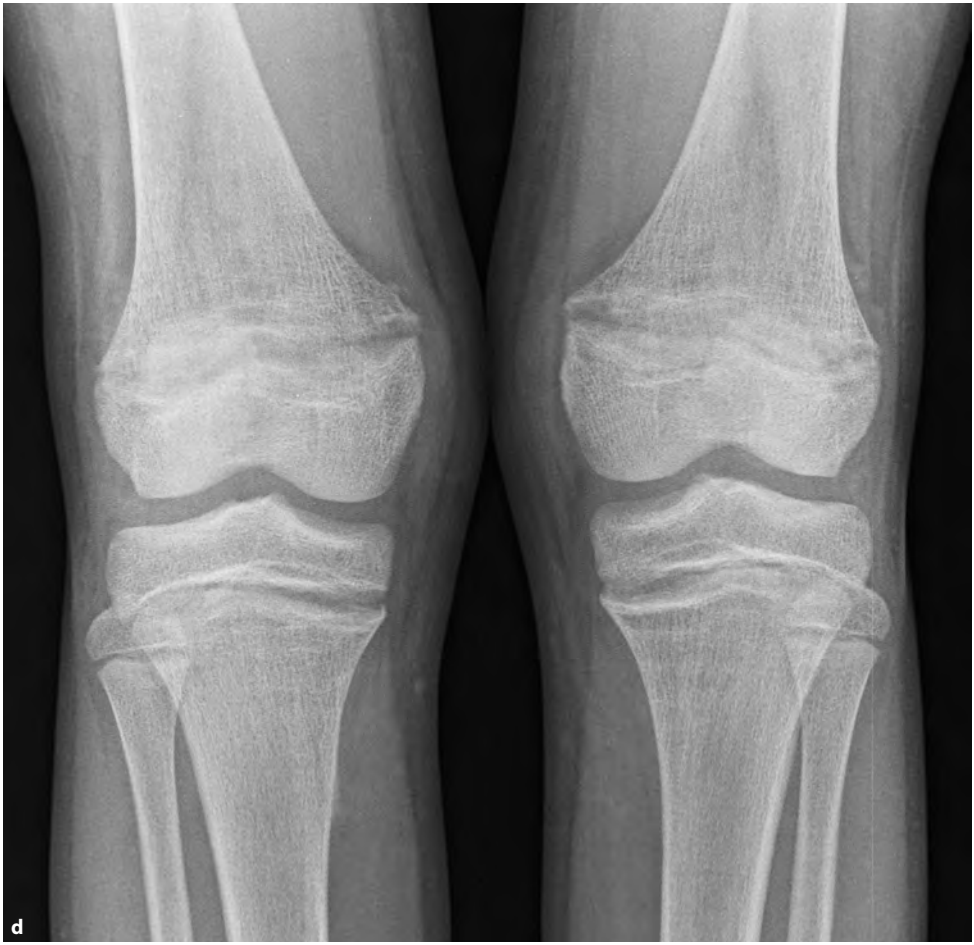


Figure 2 a–i. X-rays of children with XLH. See the wide growth epiphyses, cup-shaped enlargement and fraying of the metaphyses; the bowing and tubular shape of the long bones; the thinner fibrous cortical bone; the coarse and somewhat sclerotic bone trabeculae. **d.** 11.5 years – rachitic changes in the knee, normal tibiofemoral angle

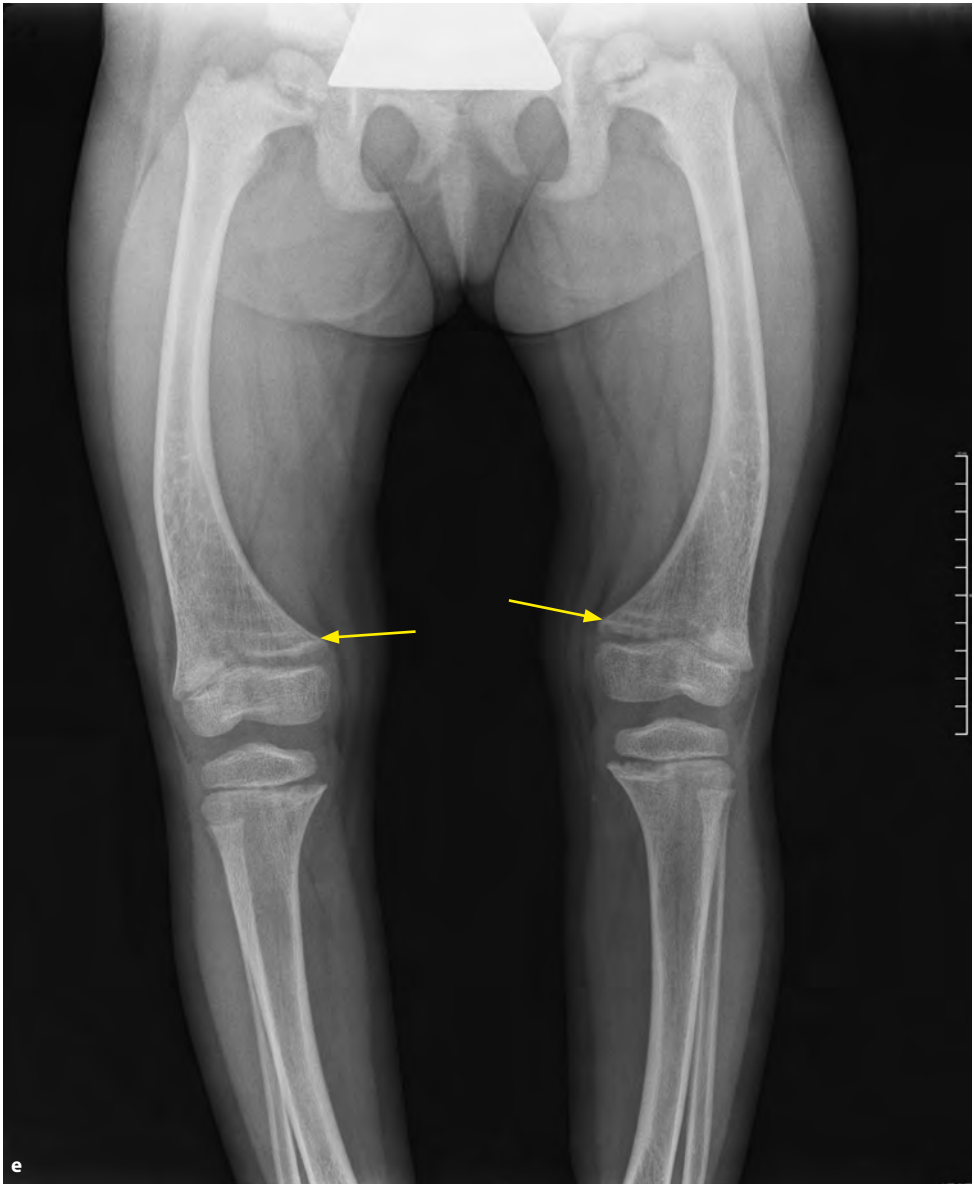


Figure 2 a–i. X-rays of children with XLH. See the wide growth epiphyses, cup-shaped enlargement and fraying of the metaphyses; the bowing and tubular shape of the long bones; the thinner fibrous cortical bone; the coarse and somewhat sclerotic bone trabeculae. **e.** 6 years – coxa vara, anterolateral varosity of the distal femurs and varosity of the distal tibiae, metaphyses are wide, frayed, and cupped; note transverse strips of increased bone density, the so--called Harris lines at distal metaphyses of both femurs (similarly as at **Figure 2 a**) – arrows

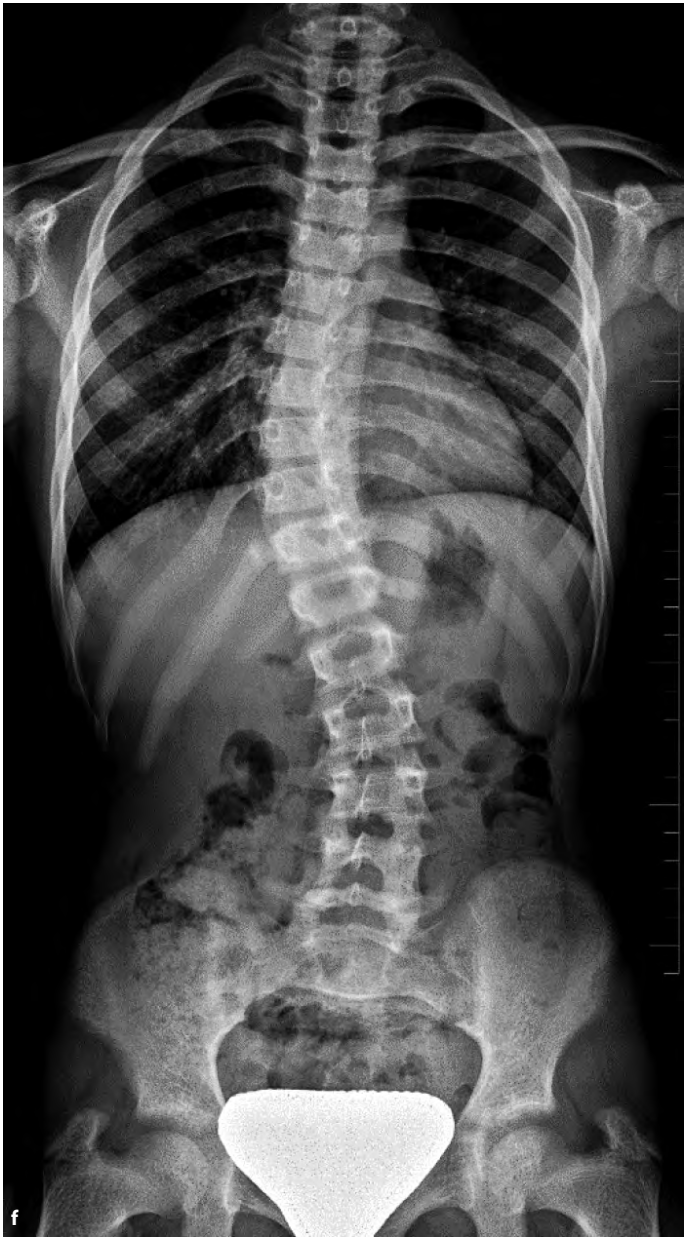


Figure 2 f. Progressive scoliosis during corset therapy – girl 10 years old, sclerosis of end plates, chest is narrow, coxa vara and rachitic changes

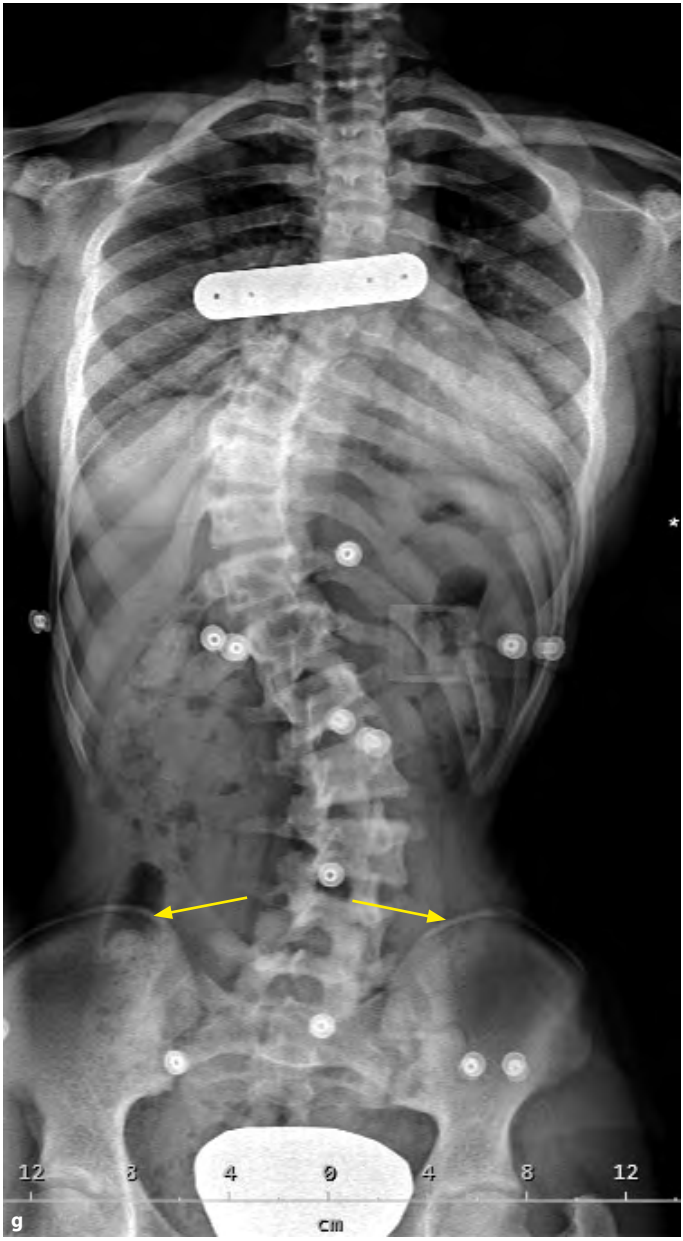


Figure 2 g. Progressive scoliosis during corset therapy – girl 14.5 years old, sclerosis of end plates and apophyses of illiac crests (arrows), chest is narrow, coxa vara and rachitic changes

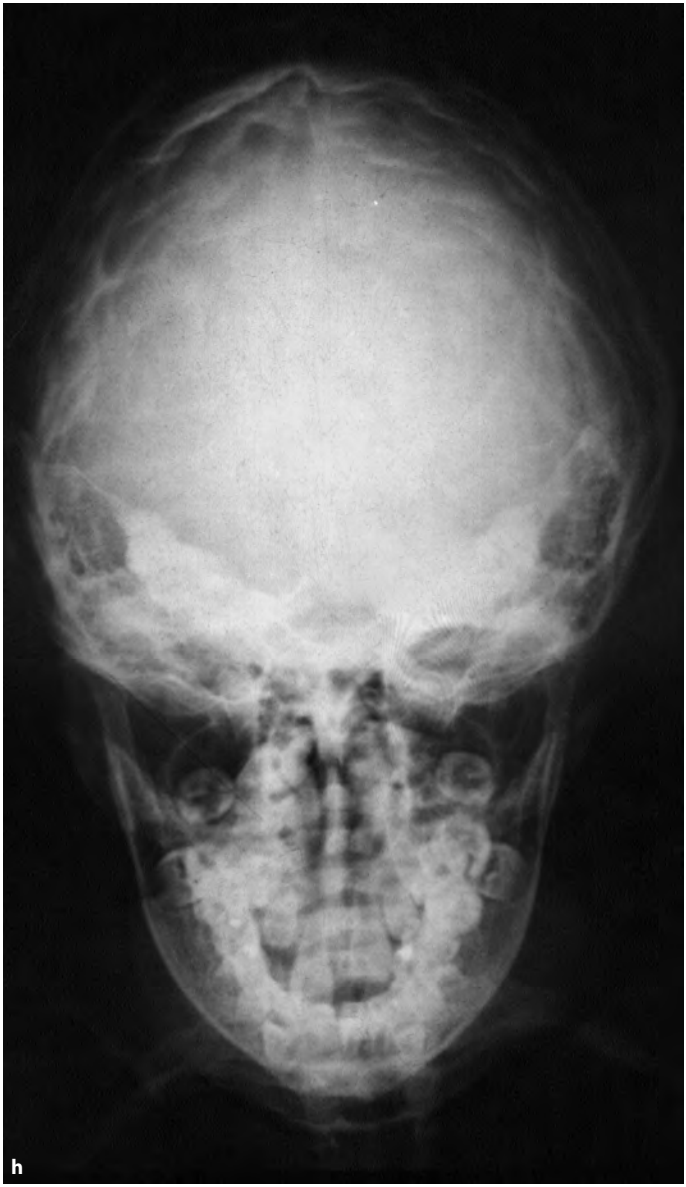


Figure 2 h. Scull AP projection: craniosynostosis – boy 6 years old, narrow dolichocephalic skull with impresiones gyrorum, so called morel mushroom skull

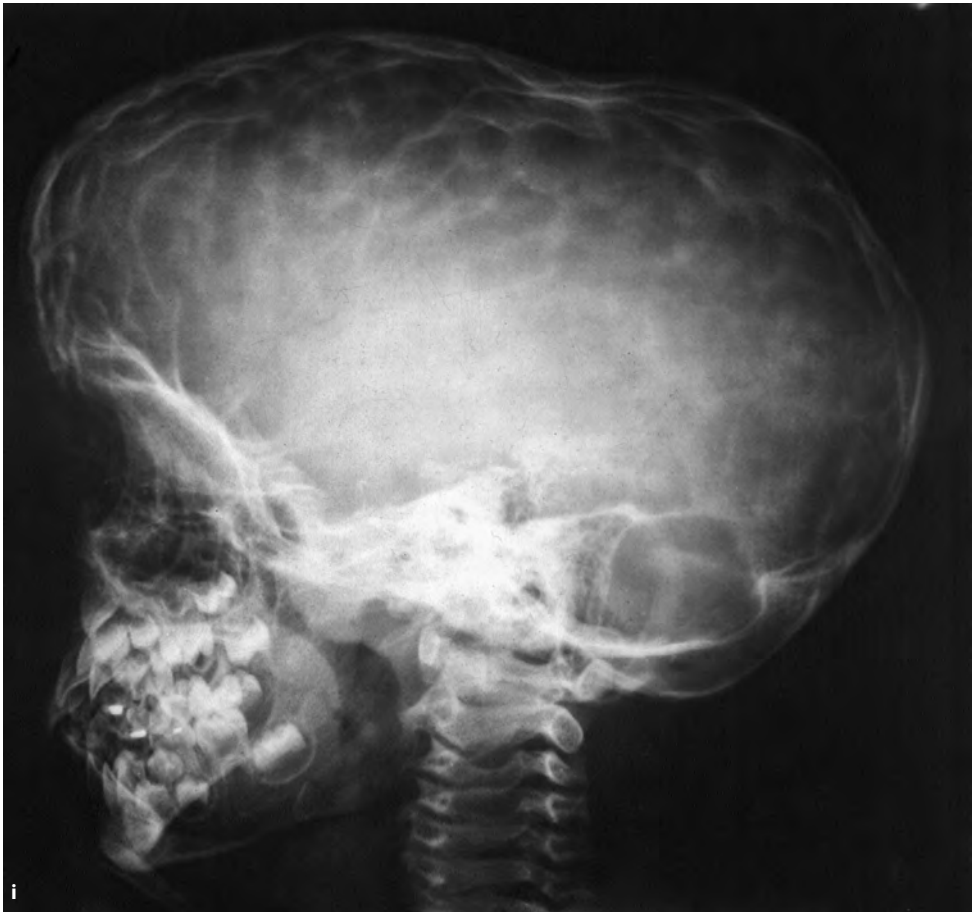


Figure 2 i. Scull lateral projection: craniosynostosis – boy 6 years old, narrow dolichocephalic skull with impresiones gyrorum and juga cerebralia, so called morel mushroom skull

pseudo fractures (fatigue or atypical fractures) of the long bones that appear as streaky lucencies across the bone without evidence of a reparative reaction – see **Figure 10 a–g** (**33, 16**); scoliosis/kyphoscoliosis of the spine and mild deformity of the thorax – **Figure 2 f, g**; heart-shaped pelvis (it may be an obstacle to spontaneous delivery); premature closure of growth plates and craniosynostosis of the sagittal suture – **Figure 2 h, i** (mutations in the FGF23 gene causes impaired endochondral and intramembranous ossification at this autosomal dominant disease) (**47, 4**); low bone density in childhood as opposed to generalized osteosclerosis of spine in adults – see **case report**; ectopic ossification at tendon and paraspinal ligament attachment sites; early osteoarthritis and spondylarthritis.

Laboratory findings (13, 21, 22, 51)

The main biochemical symptom is lower serum phosphate values depending on age (with respect to glomerular filtration rate), which may appear in the first months of life. In some patients, serum levels of phosphate may be in normal range within the first 3 month of life and later (**14**). Hypophosphatemia (**59**) is due to reduced tubular resorption of inorganic phosphate, calcium is normal or slightly reduced. In the urine, hyperphosphaturia and sometimes glycosuria is detected. In the serum, slight elevation of alkaline phosphatase (ALP), osteocalcin and marked elevation of bone ALP (BALP). In conventionally treated patients there may be an increase in parathyroid hormone (PTH) due to tertiary hyperparathyroidism. We usually detected an increase in urinary pyridinoline and deoxy-pyridinoline (**31**). In recent years, the serum markers of bone remodelling beta-CrossLaps and total procollagen type 1 are detected. FGF23 levels are most informative in untreated patients (**8**).

Histology

A typical finding of rickets is found on the ribs and metaphyses close to the knee and distant to the elbow. A disorder of endochondral ossification with the disappearance of provisional calcification and swelling of the ossification zone is observed. Disturbance of periosteal and endochondral ossification is manifested by the formation of rachitic osteophytes and osteoid seams (**29**). The degree of osteomalacia is determined by the osteoid seams, with grade 1 osteoid seams covering 20–50% of the surface of the bone trabeculae. Grade 3 is the most advanced form, where the surfaces of the trabeculae are completely covered by mostly very wide osteoid seams (**43**), see **Figure 3**.

Differential diagnoses (30, 51)

The differential diagnosis of XLH focuses on other known hereditary rickets and relies on specific laboratory findings (**51**).

Using X-ray examination, it is possible to distinguish between *Metaphyseal dysplasia of the Schmid type* – see **Figure 4** and *Hypophosphatasia*, in which the tongue-like defects of metaphyseal ossification, which appear as punched-out lesions protruding into the diaphysis, differ from the metaphyseal fraying in rickets (**40**). Typical laboratory findings are low serum alkaline phosphatase and

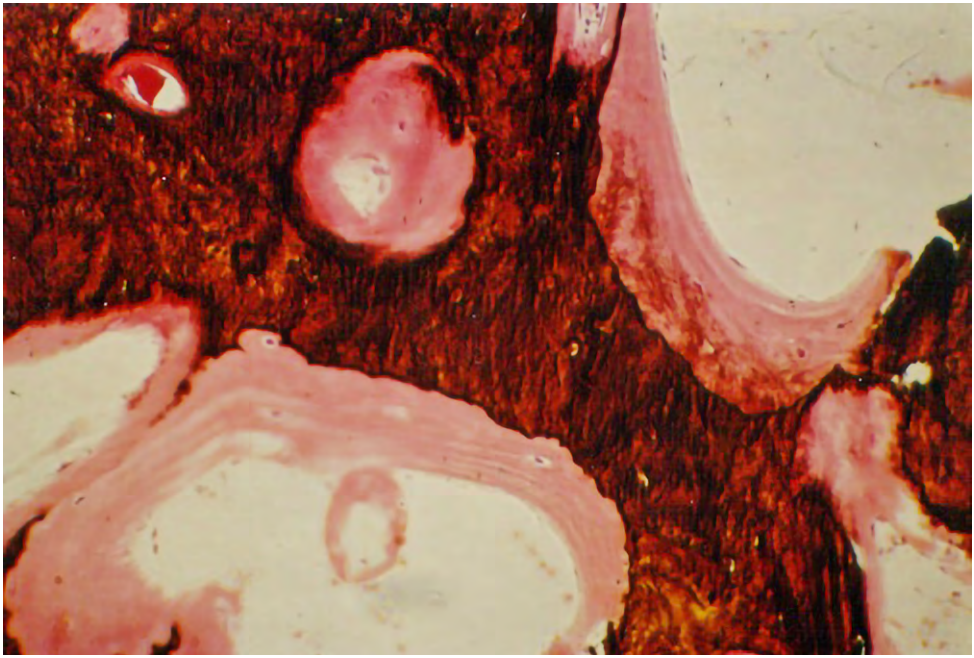


Figure 3. Histology (stained with haematoxylin-eosin) (magnifiction 100x): widening of non-ossified osteoid seams on trabeculae, grade 2 (by **Povýšil,1990**). Courtesy of Professor Ctibor Povýšil, MD, DrSc.

elevated urinary phosphoethanolamine. Hypophosphatasia is caused by mutations of the ATNSALP gene located on chromosome 1p36.1-p34 encoding the tissue-nonspecific alkaline phosphatase. The consequence is accumulation of inorganic pyrophosphate that inhibits bone mineralization and provokes ectopic calcification (**52**).

Treatment (11, 12, 30, 8, 14)

In **1972**, Glorieux et al. introduced treatment with oral phosphates (doses of 1 or more grams divided into 4–6 doses) and calcitriol (at a dose of 40–60 ng/kg/day) to prevent growth retardation and rickets in patients with XLH. Nevertheless, in most patients with XLH, this treatment is not sufficient and it is accompanied by adverse effects (nephrocalcinosis, secondary or tertiary hyperparathyroidism which promotes bone resorption) (**14**). In case of severe deformities of the long bones, corrective osteotomy is recommended to restore the biomechanical axis of the lower limb (**30**). Varosity or valgosity deformities of the knee joints in preschool age can be corrected by orthosis with preload (**32**). Severe lower limb deformities are individually indicated for surgery usually by school age. After the age of 10 (but also earlier), we individually indicate temporary medial or lateral hemi-epiphysiodesis at the region of knee joints (**39, 6**). Varosity of the distal tibia we indicate to drilling lateral hemi-epiphysiodesis and complete epiphysiodesis of the distal fibula according to

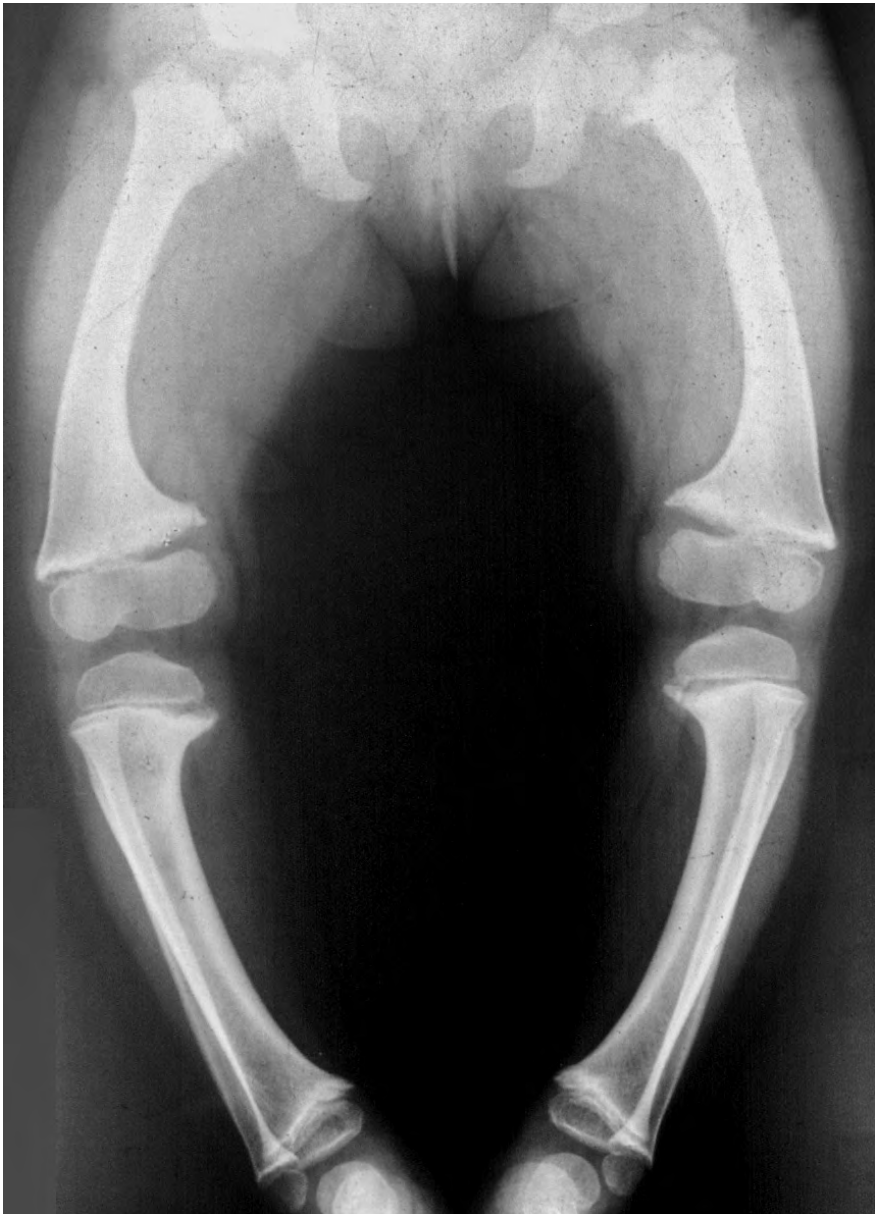


Figure 4. X-ray of the lower limbs of a 5.5-year-old girl with *Schmid type metaphyseal dysplasia*. Metaphyseal ossification is markedly irregular with splaying, fraying and cupping of the metaphyses. The physes are wide. Epiphyseal ossification centers appear normal. The acetabulum roofs are horizontal, the femoral necks short and in varus position.

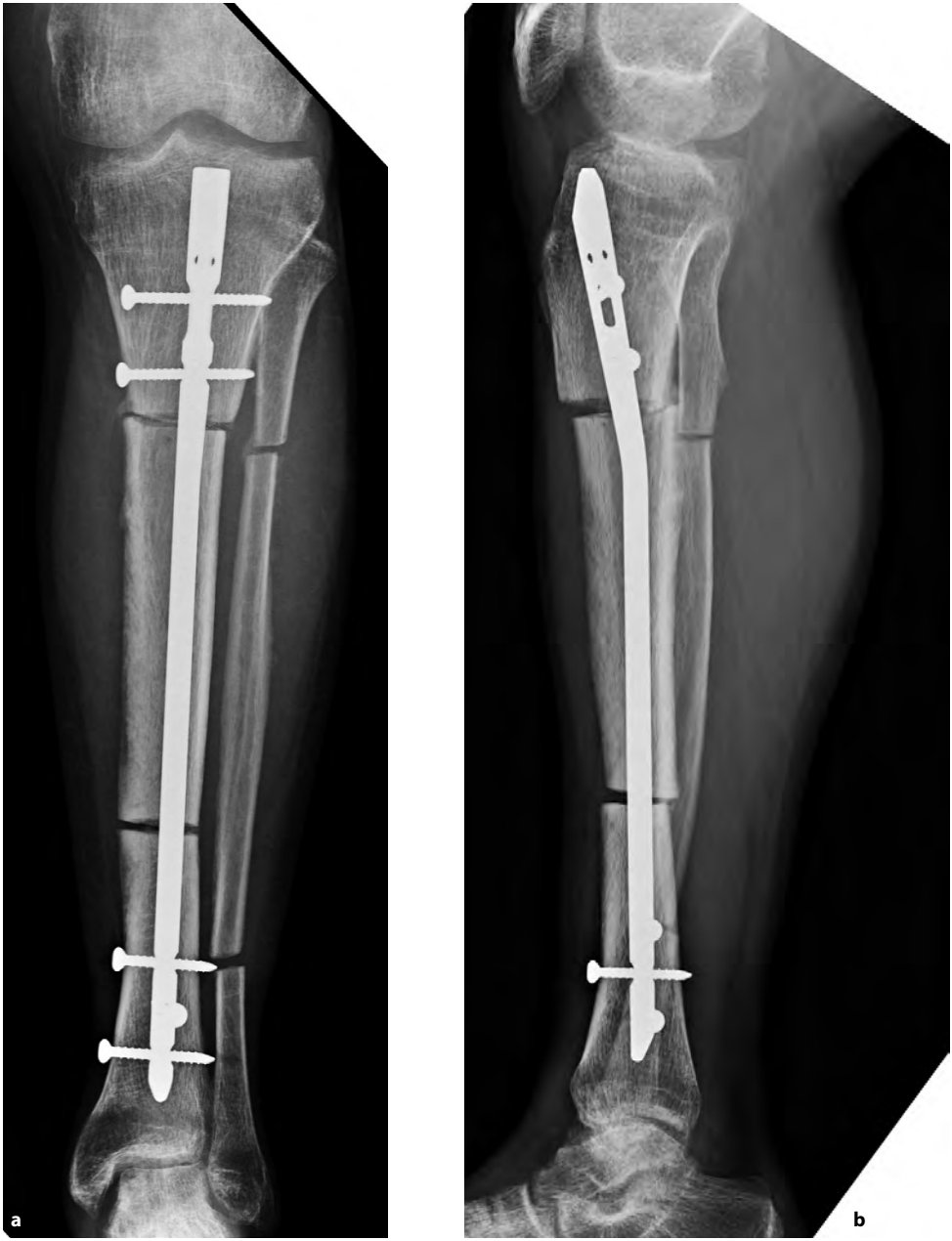


Figure 5 a, b. Adult patient, two-level osteotomy of the tibia and fibula is fixed with a secured nail.

anthropological assessment of residual growth of distal tibial and fibular physis. Severe lower limb deformities can also be treated with osteotomy and correction with use of intramedullary nails and/or external fixators with the aim of correcting in three planes. We have many years of our own experience with Ilizarov rings and unilateral devices according to Wagner also in patients with XLH (**34, 35**). In adults, corrective osteotomies and their fixation with plates, external fixation and/or intramedullary nailing are possible and still indicated – see **Figure 5 a, b**.

Hypophosphatemic rickets is one of the bone dysplasias in which research and a deeper understanding of etiopathogenesis have led to the discovery of more effective treatment. In recent years, papers presenting convincing results of causal treatment with recombinant human IgG1 monoclonal antibody against FGF23 have been published (**25, 18, 19, 20**).

Before starting therapy, it is advisable to confirm the diagnosis by molecular genetic analysis or serum levels of fibroblast growth factor 23 (FGF23) (**45, 4**), if possible. Patients should be followed up regularly by multidisciplinary teams coordinated by a specialist in metabolic skeletal diseases (**14**).

The main **aim** of the communication is to present our experience with radio-clinical diagnosis, long-term complex treatment (conventional treatment including surgical management of lower limb deformities) and interdisciplinary care of a patient with XLH from 7 years of age to adulthood. Last but not least, the authors point out the difficulties characteristic of adult patients (pseudo fractures of the lower limbs, hyperostosis of the lumbar spine, delayed healing of fractures and corrective osteotomies, etc.) and the prospective treatment with burosumab (Crysvita).

CASE REPORT

Proband comes from the mother's 5th pregnancy (2 older siblings are healthy, 2 spontaneous abortions in the 3rd month of pregnancy). Delivery at term, spontaneous, not resuscitated, birth weight 4200 g, length 56 cm, normal postpartum adaptation, thriving well. In the 1st year 3 injections of vitamin D forte (300,000 UI), later Infadin drops in a preventive dose. Preventive hip examination was normal. From 5 months to 2 years he was hospitalized several times for respiratory infections. He underwent adenotomy and tonsillectomy.

From the age of 3 years, parents observed a bowing of lower limbs. At the age of 6 he was examined for the first time at the orthopaedic department of the University Hospital in Motol. On the basis of clinical-radiological and laboratory examination (increase in total ALP and BALP isoenzyme, decrease in inorganic phosphorus and elevated osteoresorption markers), the diagnosis of XLH was made. See **Figures 6 a–e**.

During *genealogical examination*, the same diagnosis was found for the mother of the child (height 154 cm), her sister (height 157 cm), the son of the mother's sister and the mother of both affected sisters (height 155 cm) – see **Figure 7**.

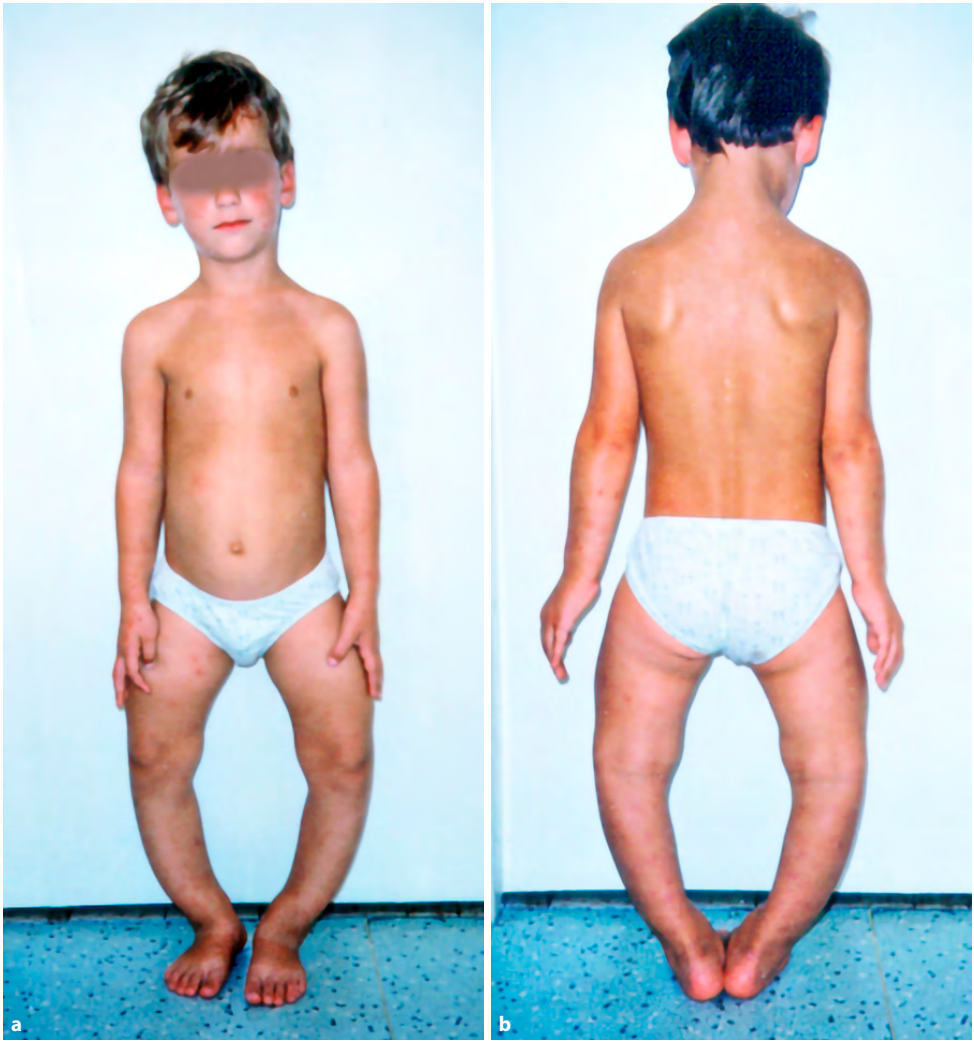
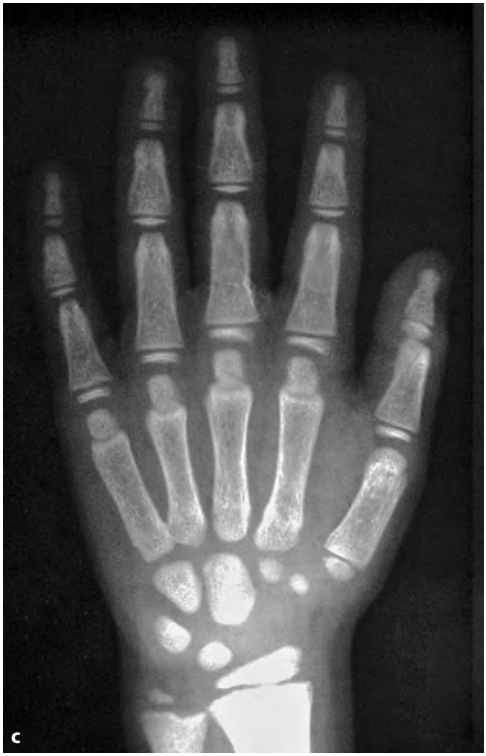


Figure 6 a, b. Phenotype and radiographs of a 6-year-old boy: short lower limbs and severe varus deformities (intercondylar distance 12 cm, malposition of the large joints of both lower limbs – external rotation of the knee joints.



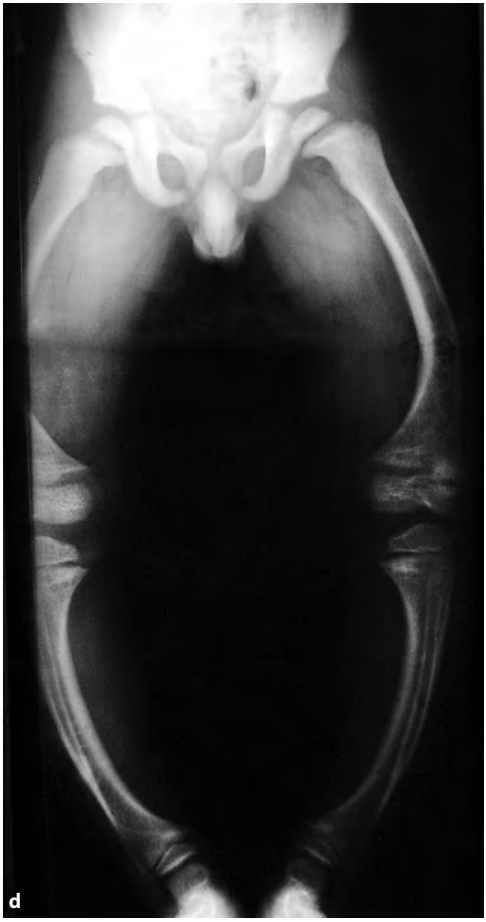


Figure 6 c, d. Rachitic changes on the hand. The cortical thinning of the metacarpals and phalanges, the distal metaphyses of the metacarpals and ulnae are slightly widened. **d.** The lower limbs with typical rachitic changes, severe varosity of diaphyses of both femurs and tibiae

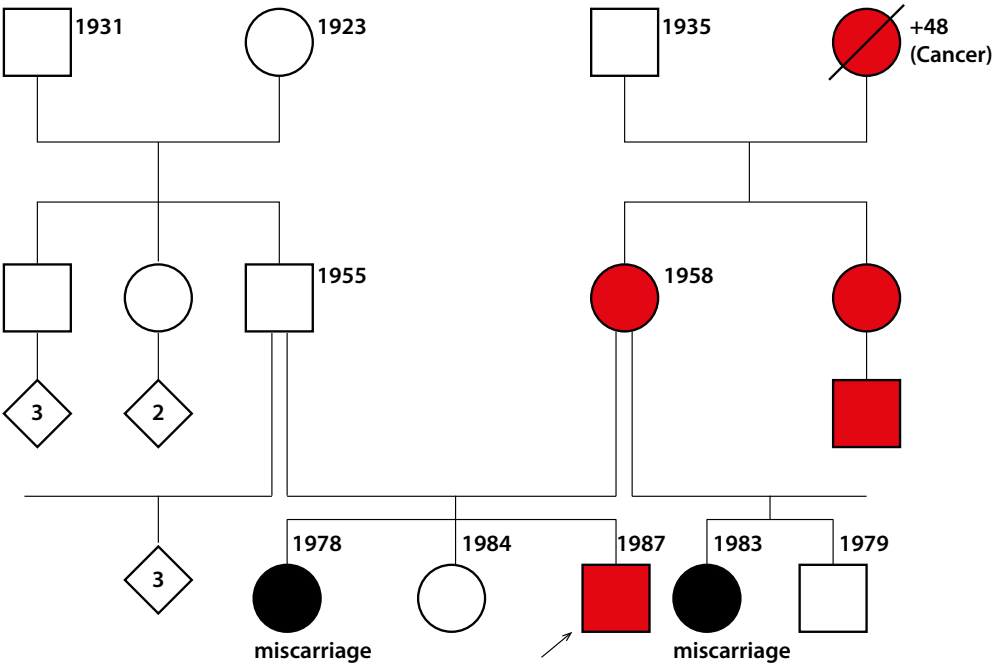


Figure 7. Pedigree showing XD-linked inheritance and transmission to the 3rd generation. The mother of proband, her sister and her son also suffer from XLH (affected marked in red)

Comprehensive treatment

Treatment with Calcitriol and inorganic phosphorus was instituted at 7 years of age. Later the treatment was administered at the Department of Paediatric and Adolescent Medicine, 1st Faculty of Medicine, Charles University in Prague by Professor Jiří Zeman, MD, DrSc.

Examination of bone metabolism markers repeatedly confirmed insufficient compensation of both phases of bone turnover (increase in total ALP and BALP isoenzyme in blood serum, increase in urinary pyridinoline and deoxypyridinoline). Hypophosphatemia was repeatedly detected despite phosphate supplementation.

At the age of 7 years and 8 months he underwent surgery on his right lower limb. Corrective segmental osteotomy of femur and tibia with intramedullary fixation according to Küntscher was performed. At the age of 8 years and 4 months, the same procedure was performed on the left lower limb at the orthopaedic department of the hospital in Pribram, where further operations were performed – see below. At the same time Küntscher nails were extracted from the right femur and right tibia – see **Figure 8**. After both surgical procedures, the operated lower limb was fixed with a unilat-

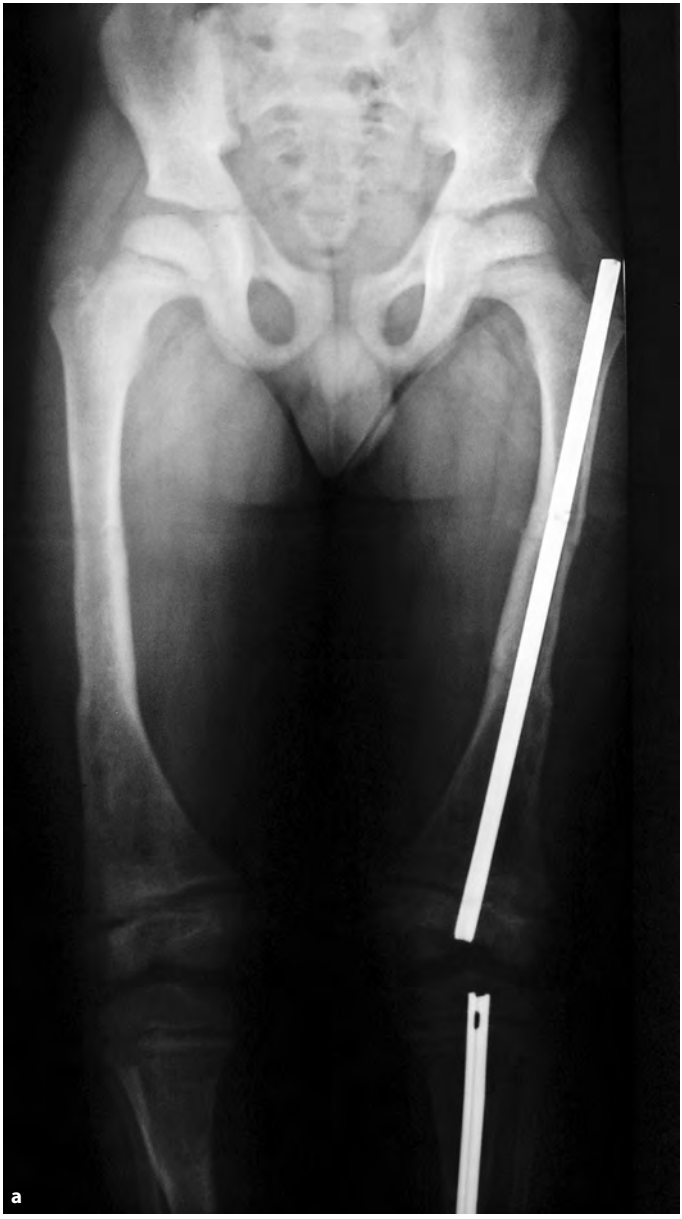


Figure 8 a. X-ray of the lower extremities at 8 years and 4 months of age after corrective three-dimensional segmental osteotomy of both femurs and tibias in two stages. The intramedullary fixation of the femur and tibia according to Küntscher can be seen on the left

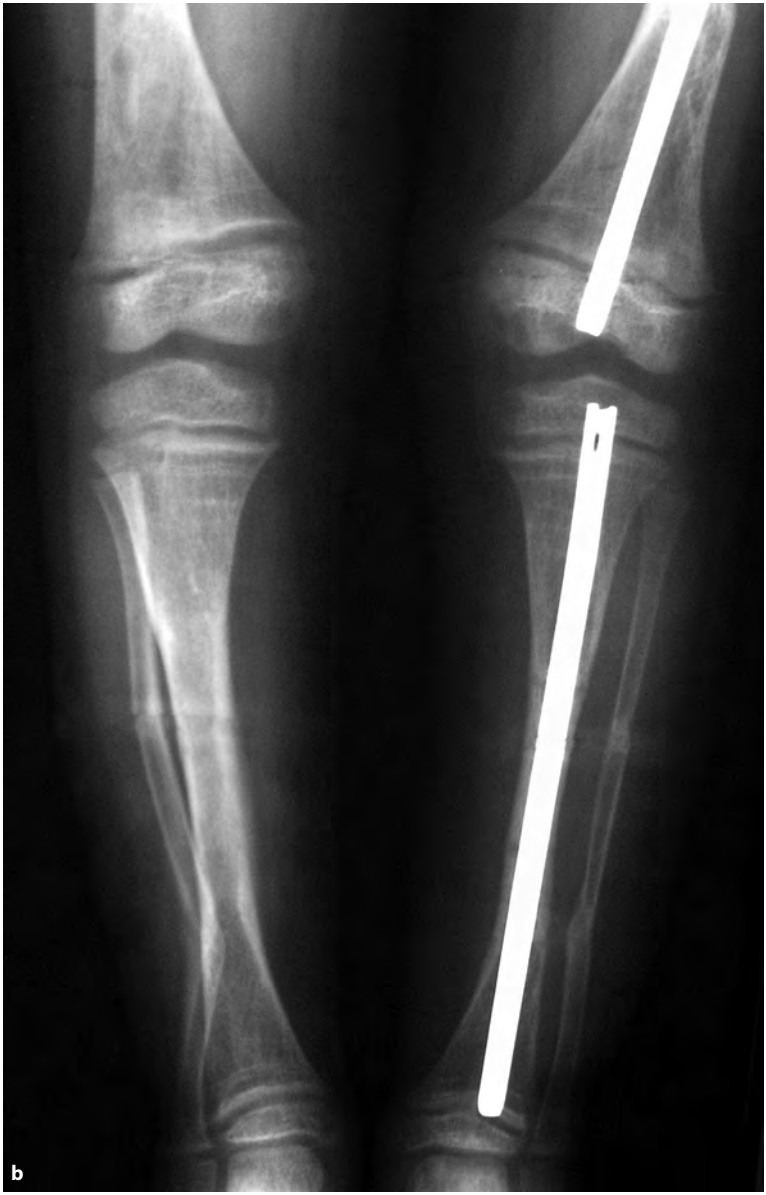


Figure 8 b. X-ray of the lower extremities at 8 years and 4 months of age after corrective three-dimensional segmental osteotomy of both femurs and tibias in two stages. The intramedullary fixation of the femur and tibia according to Küntscher can be seen on the left; extension of the zone of provisional calcification and metaphyses, slightly cupped distal metaphysis of tibia bilateralis

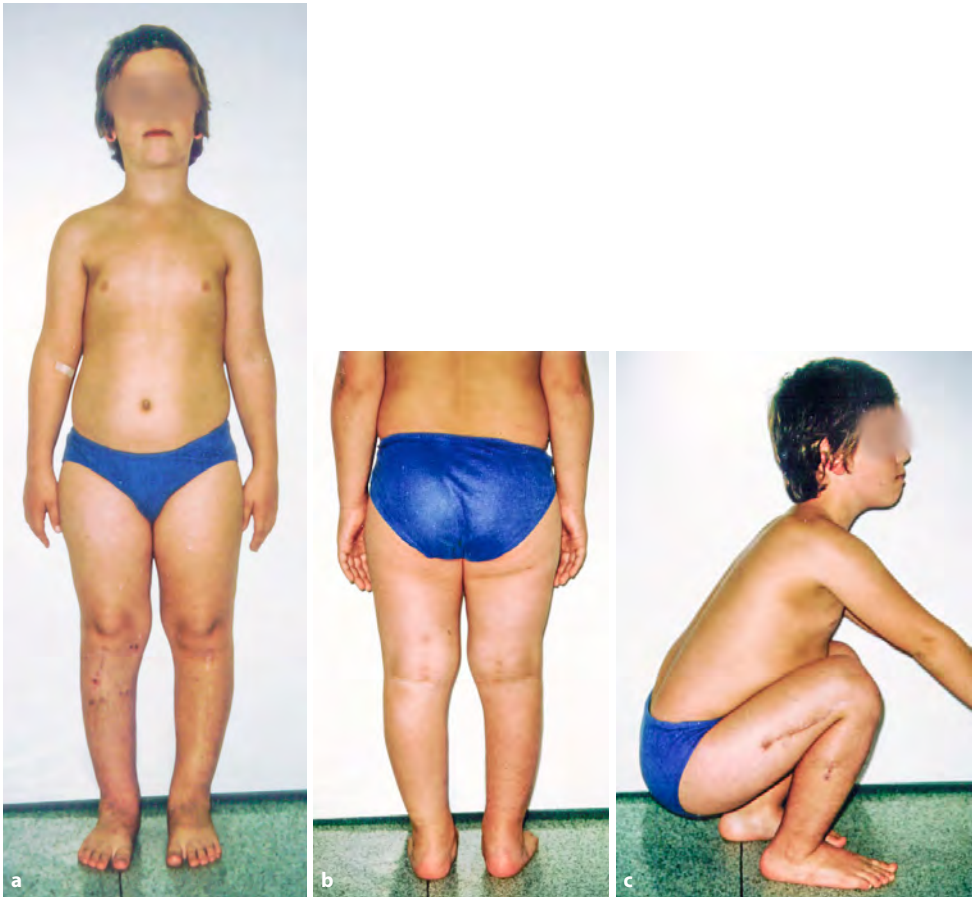


Figure 9 a–c. The result of surgical treatment at 11 years and 5 months

eral plaster cast and 1 month after surgery the patient was mobilized with a KAFO (knee-ankle-foot orthosis). At 9 years and 6 months, Küntscher nails were extracted from the left femur and left tibia.

Histological examination of bone tissue from the proximal metaphysis of the left tibia (8 years and 4 months) showed unossified osteoid seams on the spongiosis trabeculae, which is a typical picture of osteomalacia, grade 2 according to Professor Ctibor Povýšil, MD, DrSc. – see **Figure 3**.

Due to recurrence of varosity and external rotation in the right knee joint, supracondylar valgus osteotomy of the femur and external rotation osteotomy of the proximal tibia were performed at the age of 11 years. The outcome of surgical treatment at

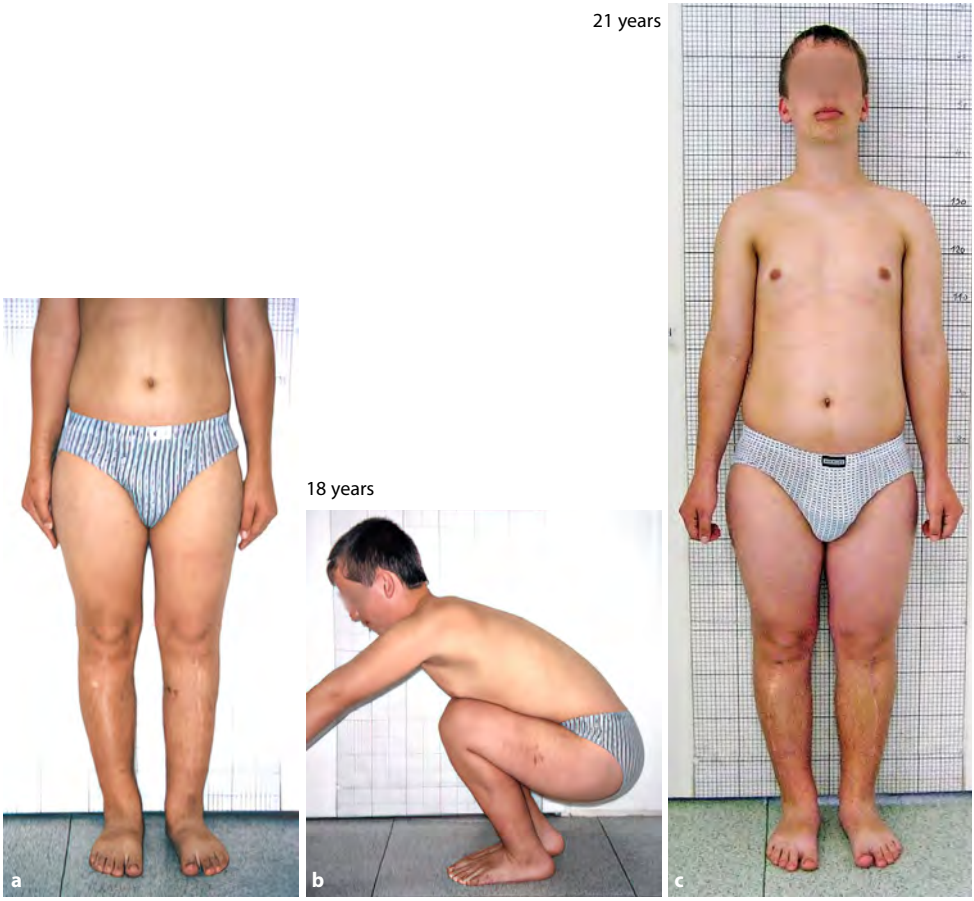


Figure 10 a–c. Outcome of comprehensive treatment at 18 and 21 years

11 years and 5 months is documented in **Figures 9 a–c**. He performed squatting without difficulty, gait was wobbly, and he was able to walk on his heels and toes. But for a mild paresis of the superficial branch of the nervus peroneus, the extension of the big toe of the right foot was slightly limited. The skeleton was robust, the trunk relatively long (0.3 SD), the shoulders absolutely narrow (-2.6 SD), highly significantly shortened limbs: lower limbs -2.8 SD, upper limbs -1.7 SD. Height 134 cm was below normal (-1.7 SD), weight 41.5 kg indicated overweight between 75th–90th percentile. Fat accumulation especially on buttocks. Prediction of height at adulthood was estimated to be around 165 cm.

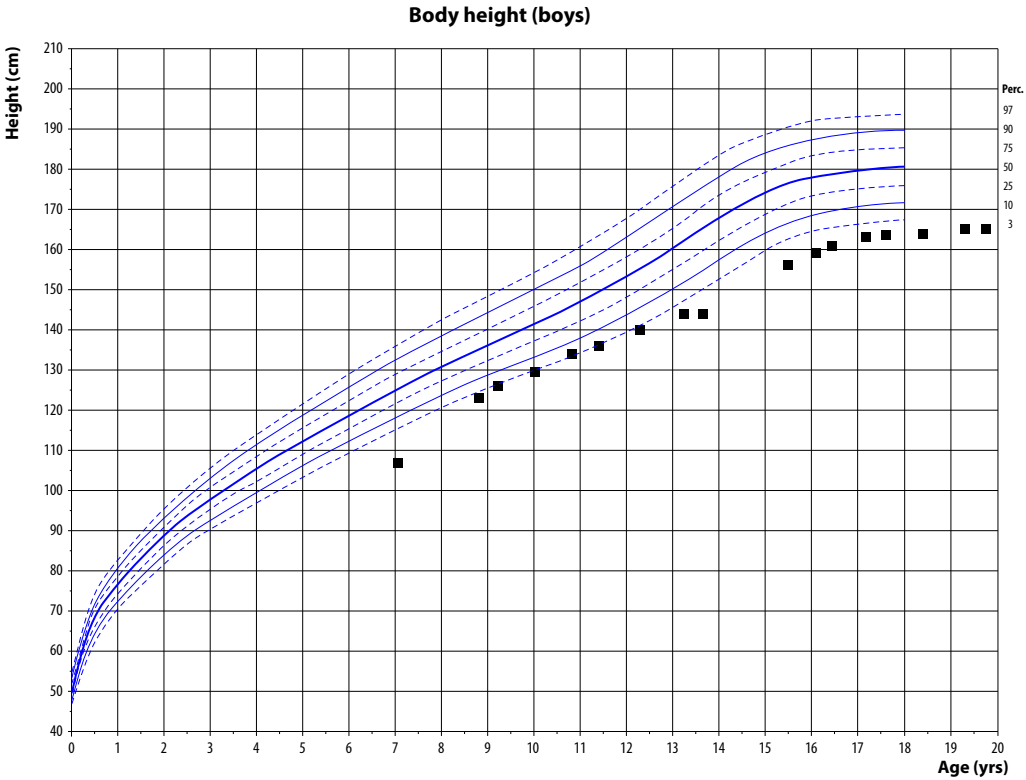


Figure 10 d. Percentile chart and the growth curve of a proband from 7 years to adulthood

At the age of 15.5 years, varosity and internal torsion of the left tibia were resolved by corrective osteotomy and at the same time derotation was performed in the proximal metaphysis of the left tibia. The operation included an osteotomy of the fibula.

The results of the complex treatment at 18 and 21 years are documented in **Figures 10a–c**, **percentile chart – 10 d** and **morphogram** at 10 and 21 years **– 10 e**.

Present illness

Since the age of 30 he has observed a small swelling on the diaphysis of the right tibia and he began to complain of pains of the right shank after long-lasting walking and standing and walking up stairs.

On examination at the age of **30.5 years**, a disproportionality of the body was found in the context of hypophosphatemic rickets, especially shorter lower limbs, very mild sinistroconvex scoliosis of

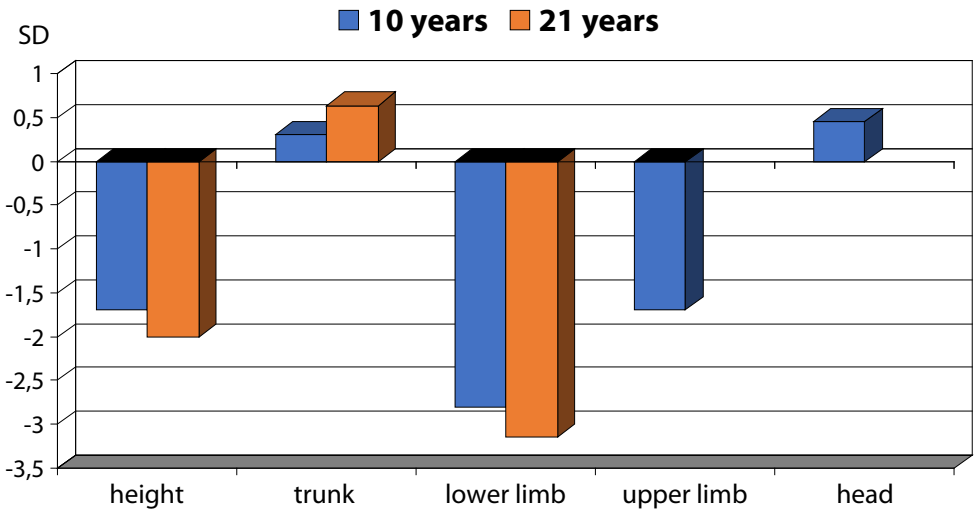


Figure 10 e. Morphogram comparing the proportionality at 10 and 21 years: The stature and especially the lower limbs are short. With growth there is a progression of shortening of the lower limbs. The head circumference is normal

the lumbar spine with shortening of the left lower limb by 1 cm and mild insufficiency of the gluteal muscles on the right. Joint hypermobility persists. In addition, malposition of the hip and knee joints (increased internal rotation in the hips) and persistent mild limitation of toe extension of the right foot (due to partial paresis of the nervus peroneus) were observed.

X-ray of the right tibia showed a cortical remodelling zone (pseudo fracture) anterolaterally in the middle of the diaphysis of the right tibia – see **Figure 11 a, b**.

On examination at **33 years of age**, the patient complains of persistent pain in the right shank and lumbar region after weight-bearing, he limped.

On radiograph of the right tibia the transverse light narrow line (arrow) at the apex of the anterolateral curvature of the cortex was still visible, no signs of healing – see **Figure 11 c–e**.

The recommended regimen of no loading of the right lower limb was insufficient for both pain relief and bone remodelling. **Figure 11 e and g** show the late repair reaction in detail (so-called "osteophyte").

Conclusion of *densitometric (DEXA) examination* in **30.5** (height 166 cm, weight 80.8 kg, BMI 29.6 kg/m^2) and **33 years (**height 165.5 cm, weight 96.1 kg, BMI 34.9 kg/m^2): Bone mineral density (BMD) in the lumbar spine was increased (hyperostosis), in the area of the left distal forearm, right and left femoral neck was in the osteopenia zone. On whole-body examination, BMD was normal, BMI – obesity

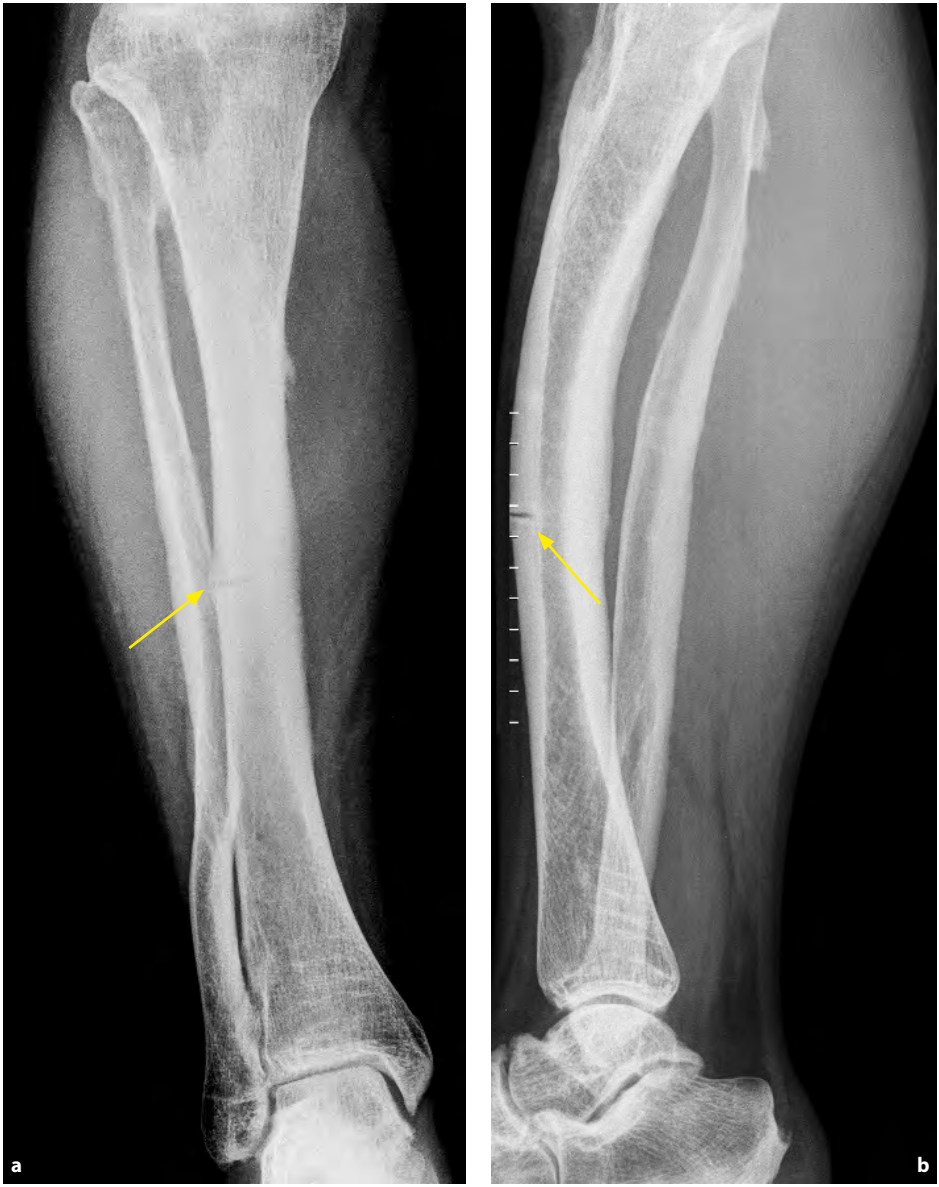


Figure 11 a, b. X-ray of the right tibia of a patient with XLH at 30.5 years; the arrow shows a clear narrow line at the apex of the anterolateral cortical curvature. This is the so-called Looser's remodelling zone (pseudofracture) in the area most stressed by compression and tension (a consequence of impaired calciophosphate metabolism).
The arrow shows the pseudofracture in detail

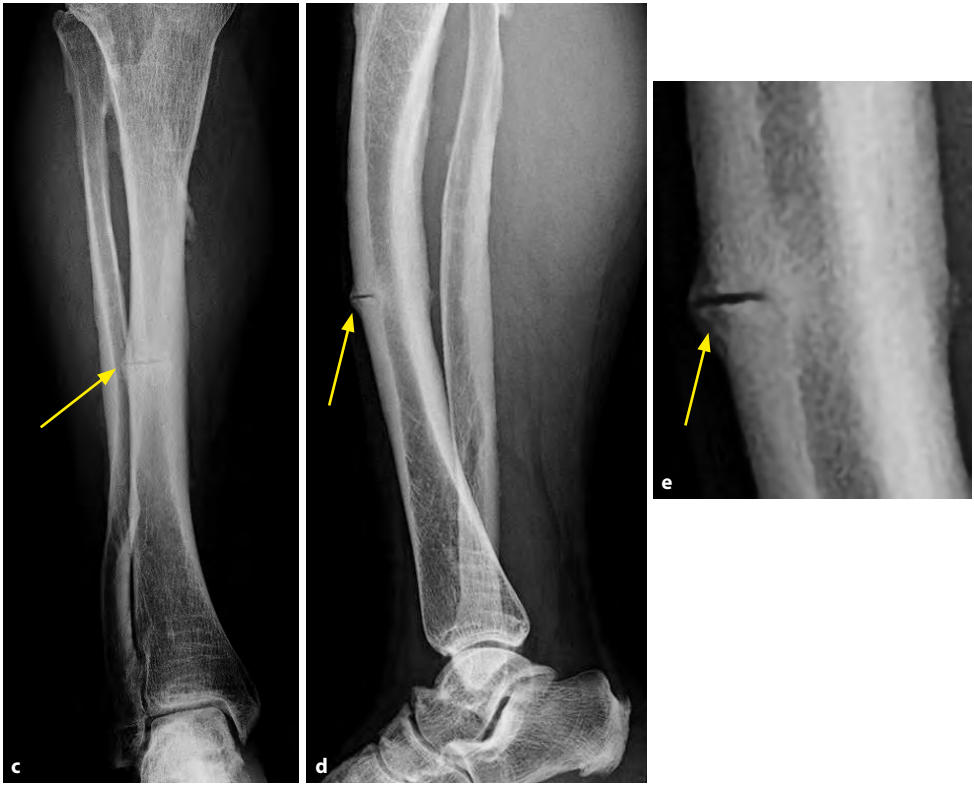
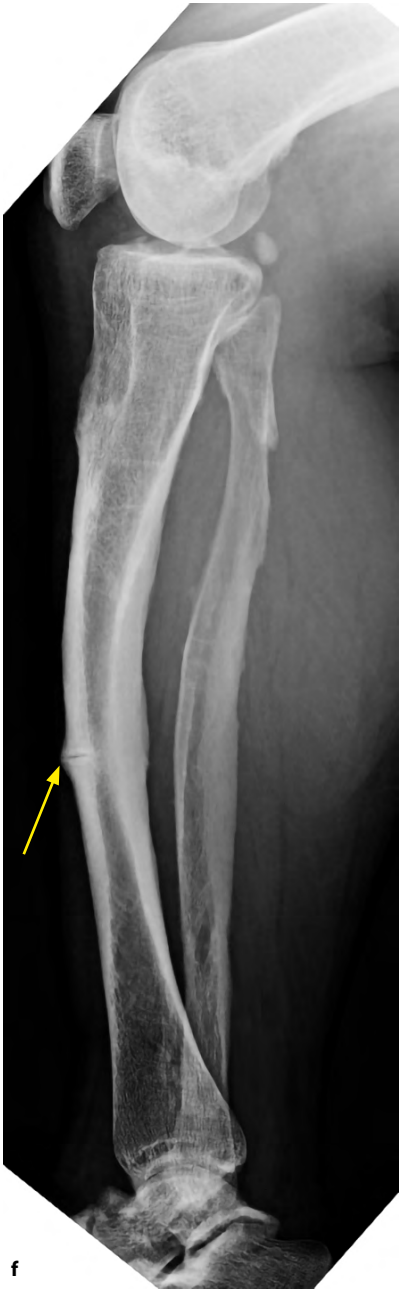


Figure 11 c–e. X-rays of the right tibia at 33 years of age show a late repair reaction (remodelling) at 2.5 years after the start of treatment. The images clearly show a transverse light narrow line (arrows) at the apex of the anterolateral cortical curvature. **e.** detail of losser's remodelling zone



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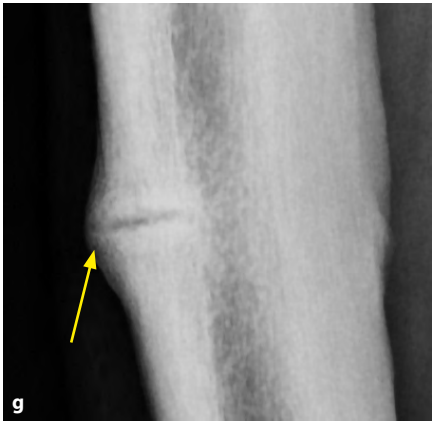

g

Figure 11 f, g. X-rays of the right tibia at 34.3 years of age show a late repair reaction (remodelling) at 3.9 years after the start of treatment. The images clearly show a transverse light narrow line (arrows) at the apex of the anterolateral cortical curvature. **g.** detail of losser's zone

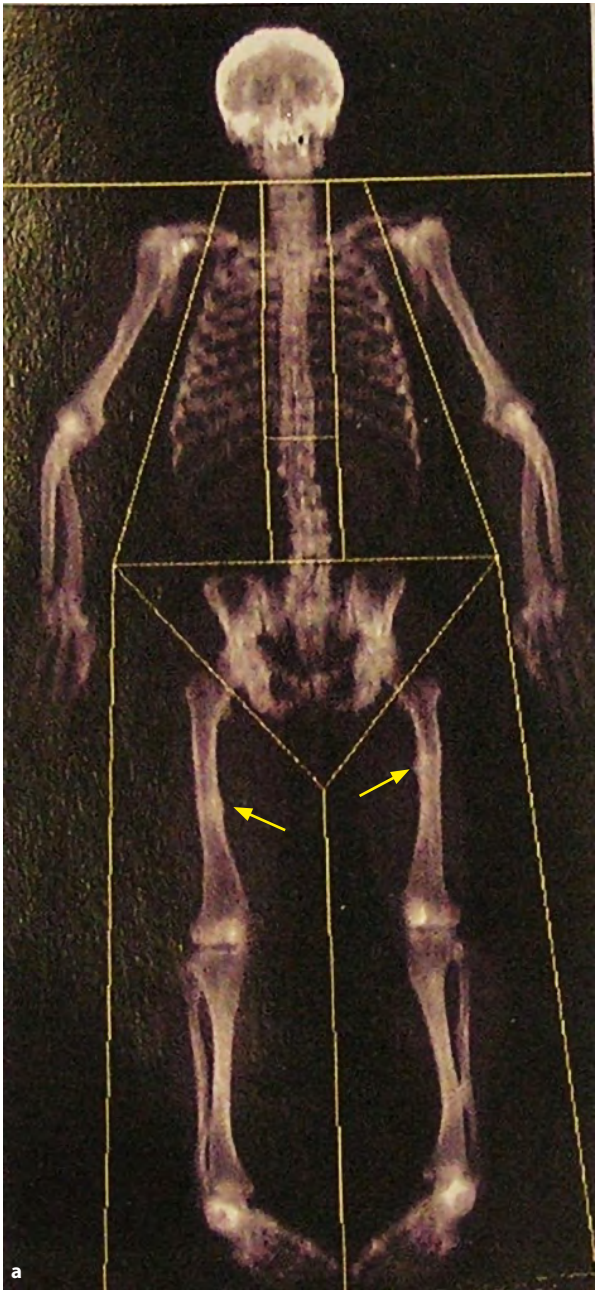

Figure 12 a. Whole-body densitometric scan at age 33 years showed suspicious pseudo-fractures in the diaphysis of the right and left femur

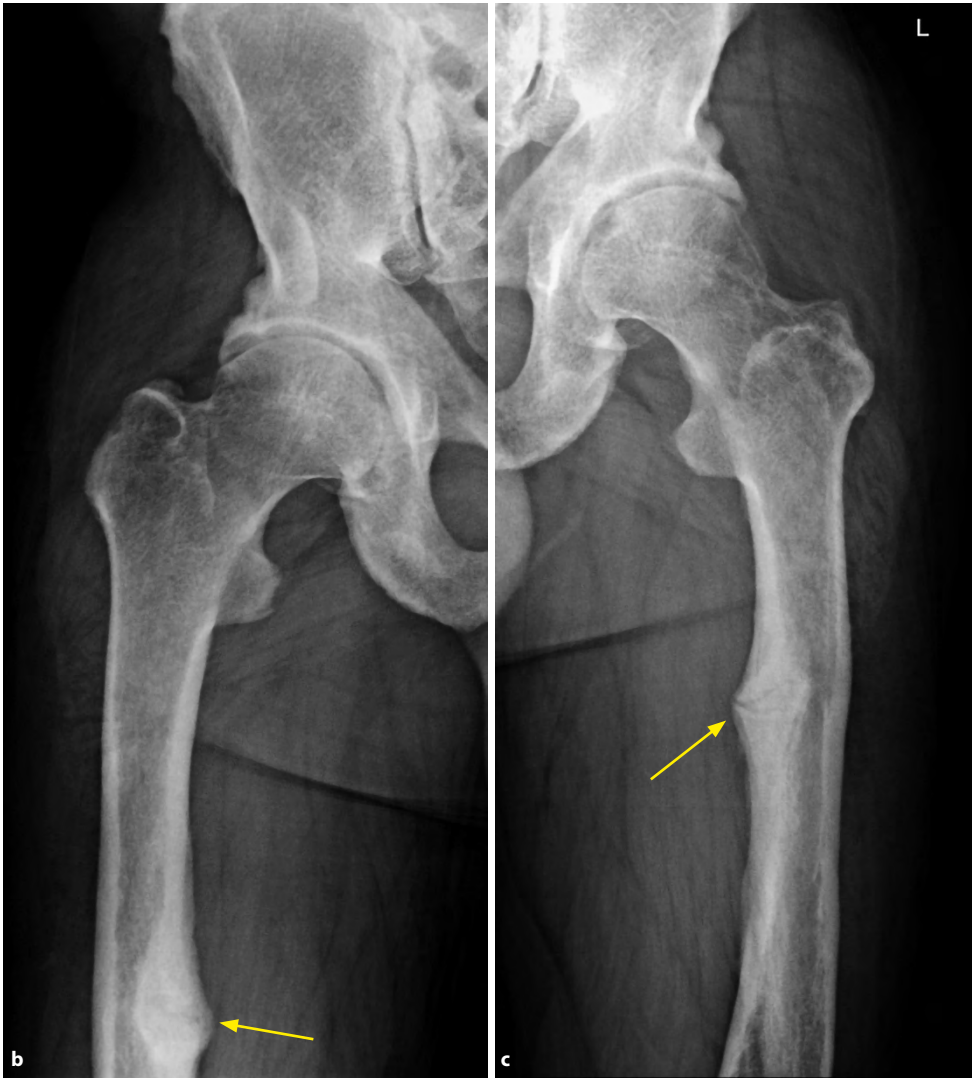

Figure 12 b, c. Radiographs verified remodelling of pseudo-fractures in the medial cortical bone of both femurs, see arrows. The arrow shows the pseudofracture in detail

zone I. On a whole-body scan at **33 years** of age, we observed suspicious pseudo fractures in the diaphysis of the right and left femur, see **Figure 12 a**.

When comparing the two most recent DEXA examinations (at 30.5 and 33 years of age), there was a statistically significant increase in density in the distal forearm (4.8%) and both proximal femurs (R/L 4.9/7.2%). BMD in the lumbar spine remained above norm (T-score 3.5 SD) without significant changes. Whole body density was above average (T-score 0.9 SD) and increased significantly by 1.3% (or 0.1 SD).

There was also a significant increase in adipose tissue content (12 686 g gained), BMI increased from 29.6 to 34.9 kg/m^2 (from overweight to obese I), and Fat mass index (FMI) increased by 12.6 kg/m^2 (i.e., 94th percentile of the US population).

Comparison of total BMD at the lumbar spine at 19.5 years (BMD 1.264 g/cm^2, Z-score was 1.8 SD), 22.5 years (BMD 1.348 g/cm^2, T/Z-score was 2.3 SD/2.3 SD), and 33.5 years (BMD 1.477 g/cm^2, T/Z-score was 3.5 SD/3.5 SD) confirmed a significant increase BMD with age.

Biochemistry results in **30.5 years**: serum phosphate lower – 0.63 mmol/l (norm 0.81–1.45), total alkaline phosphatase (ALP) higher 2.07 ukat/l (norm 0.50–2.00), normal lipid profile – atherogenicity index not elevated, parathyroid hormone normal, low 25-hydroxyvitmin D – 29.9 nmol/l (norm 50.0–200.0), 1.25-dihydroxyvitamin D normal. Markers of bone remodelling (beta-CrossLaps /CTX / and total procollagen type 1 /P1NP/) indicate increased bone turnover. Urinary excretion of calcium and phosphorus within normal limits.

Last examination at **34 years and 4 months**, the patient still complains of persistent pain in the right tibia and lumbar region after weight-bearing, with a limp. Height 165.5 cm, weight 96.1 kg (BMI 35.1 kg/m^2 – WHO classification obesity I).

On radiographs, we verified the suspected pseudo-fractures observed in the diaphysis of the right and left femur on a whole-body densitometric scan (at **33 years** of age) – see **Figures 12 b, c**.

Biochemistry laboratory results: serum phosphate low – 0.50 mmol/l (norm 0.65–1.61), uric acid elevated – 503 µmol/l (norm 220–420), ALT, AST and GGT higher, total ALP normal, lipid profile: cholesterol higher – 5.7 mmol/l (norm 2.9–5.0), LDL cholesterol 4.40 mmol/l (norm less than 3.0), non HDL cholesterol 4.50 mmol/l (norm less than 3.8), atherogenicity index not elevated (less than 4.2), parathyroid hormone 68.0 mg/l (norm 15.0–68.3), low 25-hydroxyvitamin D – 42.20 nmol/l (norm more than 75), 1,25-dihydroxyvitamin D normal. Normal markers of bone remodelling.

Elevated fibroblast growth factor 23 (p FGF 23) – 141.9 ng/l (norm 23.2–95.4).

Ultrasonographic examination of the kidneys showed no nephrocalcinosis.

Recommendation

Continue replacement therapy: calcitriol capsules daily (0.50–0–0.25 μg). Start taking phosphate solution again (4 ml 4 times a day). Still relieve the right lower limb, walking using French or trekking sticks is appropriate. Reduction diet and cycling is suitable for the purpose of weight loss.

DISCUSSION

Conventional treatment with Calcitriol and Phosphate introduced in 1972 (**11**) was beneficial in its time for the treatment of children with XLH. Our experience, consistent with literature data (**5, 3, 7, 14, 9**), confirms that conventional treatment is not sufficient to prevent growth retardation, disproportionality and progression of skeletal deformities during growth. It does not prevent recurrence of deformities after corrective osteotomies of the lower limbs during growth and the above-mentioned complications in adulthood. Imel et al. (**17**) pointed out that treatment with calcitriol and phosphate of XLH patients leads to an increase in circulating FGF 23 concentrations. Moreover, long-term supplementation with calcitriol and inorganic phosphate is often accompanied by secondary/tertiary hyperparathyroidism (**50, 27**), hypercalcemia, hypercalciuria and nephrocalcinosis (**7, 9**). Nephrocalcinosis develops in up to 80% of XLH patients who have been treated with conventional therapy. Its severity correlates closely with the dose of phosphate (**7, 57**). Nephrocalcinosis has not been reported in untreated XLH patients and is widely considered to be a result of conventional therapy associated with active vitamin D dosage (**49**).

In addition, other soft-tissue calcifications such as ocular, myocardial, and aortic valve calcification have been reported in XLH patients with persistent secondary or tertiary hyperparathyroidism and/or high dose calcitriol and phosphate treatment (**54**).

There has been no formal benefit-risk assessment for conventional therapy to show that the benefits of treatment outweigh its risks.

According to a pilot study of 29 Czech XLH patients (20 women, 9 men) with a clinico-radiological diagnosis of XLH (**61, 62**), the final height of Czech patients differs significantly from the norm (males 155.7 +/- 10 cm and females 146.4 +/- 10 cm), which is consistent with the reported height in literature of 130–160 cm (**53, 44**). Significant growth retardation occurred before the fifth year of age. Further deterioration in growth dynamics was observed at puberty. Despite conventional and surgical treatment (14 patients underwent surgery), all our patients had disproportionate habitus.

From a biomechanical point of view, it is necessary to correct lower limb deformities not only in the frontal and sagittal planes, but also in the axial plane (**36, 37**). Misalignment of the hip, knee and ankle joints is a major cause of painful walking and also of pseudo-fractures (stress fractures). The goal of surgical treatment is to have the lower limbs of equal length at the time of skeletal maturity, with neutral lower limb mechanical axes and horizontal knee and ankle joints fully mobile (**15**).

Most adult patients are obese or overweight, as documented at this paper reported case.

Between 30.5 and 33 years, BMI increased from 29.6 to 34.9 kg/m^2 (from overweight to obese I). The presented case was one of the highest patients in the Czech XLH cohort. Nephrocalcinosis and hyperparathyroidism were not detected during follow-up up to 34.3 years but densitometric examination at 30.5 and 33 years showed hyperostosis of the lumbar spine. Comparison of total BMD in the lumbar spine at ages 19.5, 22.5 and 33.5 years confirmed a significant increase with age.

Thanks to repeated surgeries during the growth period, a near – anatomical axis and normal range of motion of the lower limbs were achieved. Conventional and surgical treatment can be considered relatively successful. After the age of 30, his health deteriorated as a result of a stress fracture, which did not heal even 4 years after starting the above-mentioned conservative treatment.

The monoclonal antibody *burosumab* (Crysvita) was first licensed in February 2018 by the European Medicines Agency, then licensed by the Food and Drug Administration in the United States of America in June 2018 as the first drug targeting the underlying cause for this condition (**8**). The randomised, active-controlled, open-label study showed significantly greater clinical improvements in rickets severity, growth, and biochemistries among children with X-linked hypophosphataemia treated with burosumab compared with those continuing conventional therapy (**19, 60**).

Today, this promising pharmacological treatment in these cases is available for children with proven XLH in the Czech Republic (**56**):

1. Documented severe intolerance to standard conventional treatment (phosphate replacement and active vitamin D) or

2. Ineffectiveness of conventional treatment administered for more than 1 year according to the following criteria (it is sufficient to meet one of these criteria): (a) No improvement in growth deficit (growth rate assessed over a minimum of 6 months); growth chart position <-2.0 SD or growth chart position <-2.5 SD or growth rate at 6 months <-1 SD) or (b) evidence of rickets persists on the control native radiograph (less than 0.5 decrease in Rickets Severity Score (**58**).

The first case reports of children with XLH treated with burosumab show improvement in biochemical parameters, growth and clinico-radiological manifestations of rickets (**10, 28, 41, 55**).

The results to date with burosumab in Czech children show that with early introduction of this causal therapy, the indication for surgical treatment of lower limb deformities will be rare. Although adult XLH patients suffer from a number of complications (described above) that significantly reduce their quality of life, they are currently of secondary concern and, if treated, only with vitamin D3.

The authors point to the convincing results of causal treatment of adults with recombinant human IgG1 monoclonal antibody against FGF23, which has already been validated in double-blind studies compared with the placebo group (cited by **42**). The study demonstrates that treatment with

burosumab is well tolerated and leads to sustained improvement in serum phosphorus levels, continued healing of fractures and pseudofractures, and sustained improvement in key musculoskeletal disorders.

Haffner et al. (**14**) recommend considering treatment with burosumab in adults with X-linked hypophosphatemia (XLH) with persistent bone and/or joint pain due to XLH and/or osteomalacia that limits activities of daily living; osteomalacia-related pseudofractures or fractures; poor response or refractory to conventional treatment. However, burosumab should not be administered with conventional therapy, in patients with phosphate levels within the age-normal reference range prior to initiation of therapy, or in the presence of severe renal impairment.

The patient presented is an example of an adult patient with XLH who is indicated for treatment with burosumab even though conventional and surgical treatment was relatively successful in childhood.

The availability of burosumab treatment is promising for improving the quality of life not only for children but also for adults.

Conclusions and perspectives

In patients with XLH and other hereditary rickets, deterioration of bone structure and reduced skeletal strength due to impaired calcium and phosphate metabolism persist throughout life, causing slowed disproportionate growth, skeletal deformities, prolonged healing of fractures and corrective osteotomies, and pseudo-fractures. Calcium and phosphate metabolism are disturbed during whole life.

Adult patients suffer from generalized osteosclerosis of the spine. Increased bone hardness leads to the development of premature osteoarthritis of the weight-bearing joints of the lower limbs, spondylosis and spondylarthritis of the spine with vertebrogenic algic syndromes.

With other complications such as impaired mobility, joint and muscle pain, dental abscesses, hearing impairment and others, affected patients have difficulty in obtaining adequate education, starting a family and later on limited choice of employment and early disability.

Conventional treatment is not sufficient to prevent growth retardation, disproportionality and progression of skeletal deformities during growth, nor does it prevent recurrence of deformities after corrective osteotomies of the lower limbs and the above complications in adulthood. In addition, conventional treatment brings serious adverse side effects, i.e. hyperparathyroidism and nephrocalcinosis.

The U.S. Food and Drug Administration (FDA) has approved Crysvita (burosumab-twza, a human IgG1 monoclonal antibody against FGF23), the first drug approved to treat adults and children 1 year of age and older with X-linked hypophosphatemia (XLH).

We hope that this promising pharmacological treatment will be available for all children in the Czech Republic with proven XLH from preschool age and also for adults with XLH in the treatment of fractures, corrective osteotomies, for the treatment of stress fractures and hyperostosis and other bone damage due to metabolic bone disease. Treatment with burosumab will undoubtedly prevent the adverse effects of conventional vitamin D3 and phosphate therapy, namely nephrocalcinosis and hyperparathyroidism.

So far, XLH remains a multisystem disease that evolves over time, and multidisciplinary care for XLH patients is needed, involving physicians, physiotherapists, dentists and social workers, and collaboration with patient group representatives. Current views and recommendations regarding the comprehensive treatment of hypophosphatemic rickets will undoubtedly be updated in the near future based on new findings on natural history of the disease and further experience with burosumab treatment.

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MNOHOČETNÁ EPIFYZÁRNÍ DYSPLAZIE, TYPY 1, 4 A 5 V KLINICKÝCH PŘÍPADECH: SROVNÁNÍ RADIOKLINICKÝCH ZNAKŮ S GENETICKÝM POZADÍM

MULTIPLE EPIPHYSEAL DYSPLASIA (MED), TYPES 1, 4 AND 5 IN CLINICAL CASES: COMPARISON OF RADIO CLINICAL FEATURES WITH GENETIC BACKGROUND

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SUMMARY

Multiple epiphyseal dysplasia (MED) is a clinically and genetically heterogeneous skeletal dysplasia caused by pathogenic variants in the genes encoding important cartilage extracellular matrix proteins, enzymes and transporter proteins.

The authors compare the clinical, anthropological and radiological findings in three index cases of bone dysplasia in which molecular genetic testing confirmed MED types 1, 4 and 5. In case 1, molecular genetic testing found an unpublished variant c.1450T>C in the *COMP* gene in the heterozygous state. Pathogenic variants in *COMP* gene are associated with Pseudoachondroplasia (PSACH) and MED type 1 with existing phenotypic continuum between both dysplasias. This case represents the most severe phenotype among our patients. In this case the authors demonstrate the outcome of comprehensive treatment and care. In case 2, genetic testing revealed a heterozygous variant of the *MATN3* gene c.437T>C, which may be associated with MED type 5. The boy is being treated with growth hormone for the indication IUGR/SGA. Although the growth rate has been favourable so far, the actual effect of the treatment can only be assessed after the final height has been reached. In case 3, genetic testing of two siblings revealed a homozygous pathogenic variant c.1957T>A in the *SLC26A2* gene, which may be associated with recessive MED type 4.

Key words: multiple epiphyseal dysplasia type 1, 4 and 5, clinical, anthropological and roentgenologic findings, molecular genetic testing, gene, *COMP, MATN3, SLCA26A2,* variant.

INTRODUCTION

Multiple epiphyseal dysplasia (MED), known originally also as Hereditary dysplasia epiphysealis multiplex (**17**), is generalized **skeletal dysplasia** associated with significant morbidity. The main *clinical findings* are weight bearing joint pains, prominent joints with restricted mobility, waddling gait, contractures, accentuated thoracic kyphosis and lumbar lordosis with back pains, genua valga or vara and short stature. *Radiological features* comprise delayed, irregular mineralization of the epiphyseal ossification centres of long bones and of the carpal and tarsal bones. The epiphyses may change from small and rounded to flattened-out. Vertebral bodies are usually unaffected or show modest irregularities (**36**).

In the past, the division into a more severe Fairbank and a milder Ribbing type was widely used (**8, 31**). Currently, MEDs are divided according to **genetic background**.

Aetiology and pathogenesis

MEDs are caused by pathogenic variants (i.e. mutations) in genes encoding proteins involved in formation of cartilage extracellular matrix and its integrity: *COMP*, *COL9A1*, *COL9A2*, *COL9A3*, *MATN3* (autosomal dominant transmission, AD) and *SLC26A2* and *CANT1* (autosomal recessive transmission, AR) (**Tab. 1**) (**4, 5, 6, 39, 14, 1**).

Multiple epiphyseal dysplasias

gene	Mildphenotype	Severe	Lethal
COMP	**MED 1** AD	Pseudoachondroplasia AD	
COL9A2	**MED 2** AD Stickler syndrome 5		
COL9A3	**MED 3** AD Intervertebral disc disease AD		
SLC26A2	**MED 4** AR	Diastrophic dysplasia AR	Achondrogenesis 1B Atelosteogenesis II
MATN3	**MED 5** AD Osteoarthritis susceptibility 2 AD	Spondyloepimetaphyseal dysplasia AR	
COL9A1	osteoarthritis **MED 6** AD Stickler syndrome 4		
CANT1	**MED 7** AR	Desbuquois Dysplasia 1 AR	

Table 1: The table shows disorders of cartilage ECM (excluding collagenopathies II), genes involved in these processes, various mutations can cause different phenotype – mild, severe, lethal. The most frequent cause of dominant MED is mutation in *COMP*. Other mutations in *COMP* result in PSACH (There is some overlap in symptoms). Sulfate transporter – MED type 4, other mutations diastrophic dysplasia, complete loss of enzyme function – lethal dysplasias.

COMP mutations resulting in MED type 1 is the most frequent form in most populations. It is allelic to pseudoachondroplasia (PSACH). *MATN3* mutations are associated with MED type 5 that represents the second most common form particularly common in the Asia population (**36**).

Cartilage oligomeric matrix protein (COMP) is non-collagenous protein binding other extracellular matrix (ECM) proteins and catalysing polymerization of type II collagen fibrils. It plays a role in regulation of chondrocyte proliferation. *COMP* mutations lead to the improper folding of the COMP protein and to retention of the abnormal COMP protein and type IX collagen in the endoplasmic reticulum which causes premature death of chondrocytes. It results in the failure of endochondral ossification and diminished growth of long bones. Additionally, ECM contains minimal COMP, and little type IX collagen. This deficiency results in easily eroded abnormal joint cartilage and painful osteoarthritis. Mutations in the gene encoding COMP cause two skeletal dysplasias, PSACH and MED (**29, 30, 12, 39, 19**).

Type IX collagen belongs to the Fibril-associated collagens with interrupted triple-helices (FACIT) collagens where the domains formed by the classical triple helices are interrupted by non-helical domains. These collagens mediate the interconnection of fibrillar collagens with other parts of extracellular matrix (**28**). Type IX collagen contributes to the stabilization of the fibrillar collagen network in the cartilage matrix and the anchorage of matrilin 3 and proteoglycans, which controls the diameter of collagen fibrils (**10**). Mutations in type IX collagen can predispose individuals to MED type 2 (*COL9A2*), 3 (*COL9A3*) and 6 (*COL9A1*), Stickler syndrome 4 (*COL9A1*), Stickler syndrome 5 (*COL9A2*) and intervertebral disc disease (*COL9A3*).

Matrilin-3 as an adaptor protein, is an essential component during cartilage development and ossification. It binds to collagen IX to form a filamentous network around cells (**39, 33**). In addition, it regulates chondrocyte proliferation and hypertrophic differentiation by interactions with transforming growth factor β (TGF-β), and bone morphogenetic protein 2 (BMP2) (**27**). Mutations in *MATN3* gene cause MED type 5, osteoarthritis susceptibility 2 (both AD transmission) and spondyloepimetaphyseal dysplasia (AR transmission).

Proteoglycans, especially aggrecan, gives articular cartilage its ability to resist compressive loads. The other smaller proteoglycans (decorin, biglycan) are characterized by their ability to interact with collagen and contribute to the integrity of cartilage matrix. Proteoglycans possess sulphated glycosaminoglycan chains. *SLC26A2* gene encodes sulphate transporter which is essential for normal cartilage formation. As with other enzymes, the disease is autosomal recessive. Various mutations in *SLC26A2* cause both MED type 4 and diastrophic dysplasia (**3, 2**).

CANT1 (Calcium activated nucleotidase 1) is a gene encoding soluble nucleotide enzyme belonging to apyrase family which plays role in calcium ion binding and pyrophosphatase activity. Among its related pathways is cartilage proteoglycan biosynthesis (**11**). However, the exact function of the protein because of the complexity of its role is not fully understood. Diseases associated with *CANT1* mutations include Desbuquois Dysplasia type 1 and MED type 7 (**1**) both with AR inheritance pattern.

Ongoing research shows that some patients with the clinical and radiographic phenotype of MED do not have mutations in these genes, suggesting the presence of causative genes other than the 7 genes mentioned above (**13, 39, 15, 33**).

Major differential diagnosis

Differential diagnosis of MED comprises bilateral Legg-Calvé-Perthes disease, hypothyroidism, spondyloepiphyseal dysplasia (congenita and tarda types), various juvenile arthropathies, chondrodysplasia punctata (Conradi-Hünermann type), PSACH (mild forms), and type 2 collagenopathies (**36, 23**). MED has also been described in coincidence with myopia and deafness, or with microcephaly and immunodeficiency, microcephaly, mental retardation and nystagmus, and other MED syndromes e. g. MED with deformities of the fingers, MED with brachydactyly of the hands and feet, epiphyseal dysplasia localized to the knee joints, hip joints, MED with pedes equinovari, etc. (**24, 20, 38, 22, 23**).

Recessive MED type 4 can be differentiated from dominant types of MED by subtle radiographic differences: flat rather than small capital femoral epiphyses, flat metatarsal and phalangeal epiphyses, clubfeet, and double-layered patella – see **Figure 1** (**36**).

The aim of the study is to compare the clinical and anthropological findings and radiological picture with the genetic background of MED type 1, 4 and 5 in cases diagnosed at our institutions. In MED type 1 (case 1), the authors demonstrate the outcome of comprehensive treatment and care.

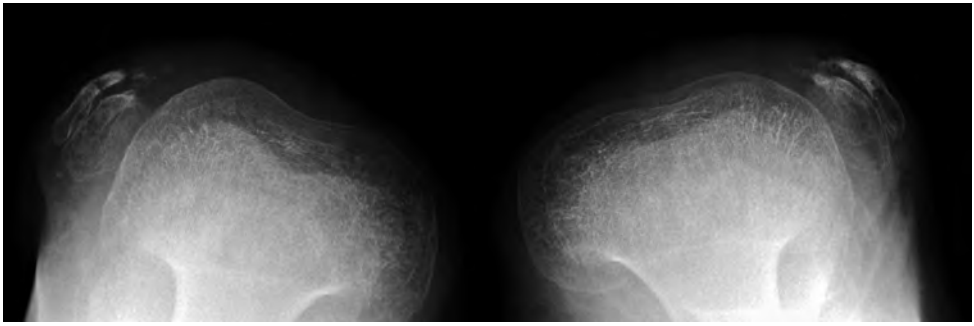


Figure 1: X-ray – axial view of the patellae in a 10-year-old boy with MED. Dislocated two-layered patellae are typical of recessive MED type 4, as demonstrated by genetic testing in this patient.

CASE 1

The girl was born from pregnancy after intrauterine insemination. The birth was at term with 2750 g and 47 cm – at the lower end of the norm for the gestational age. Except for worse hip joint mobility, she was free of any signs of congenital defects. After the age of one year, the mother observed an abnormal gait. Therefore, she was examined in orthopaedic unit in Brno. *Spondylometaphyseal dysplasia* was suspected. The first visit to our department took place when the patient was 5 years 9 months old. The phenotype of the affected girl is shown in **Figure 2 a–c**; radiological examination of the hip, knee and ankle joints showed epiphyseal and mild metaphyseal dysplastic changes – see **Figure 3 a–c**. Dysplastic changes on the hand are shown in **Figure 3 d**.

Later, mild platyspondyly on the spine was demonstrated. The dens epistrophei was correctly shaped. According to radiological and clinical findings. **Epimetaphyseal dysplasia with minimal vertebral changes** was suspected.

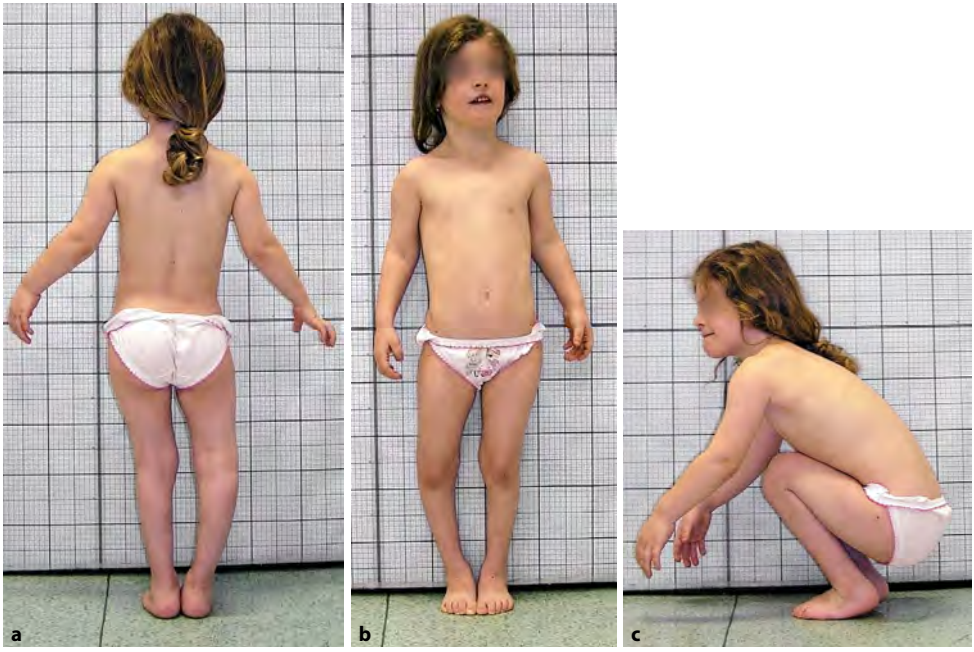


Figure 2 a–c. Case 1 a girl 5 years and 9 months old. The patient had varosity of the proximal right tibia, squat without restriction, hyperextension of the right knee joint, flexion contracture of the elbow joints 20 degrees. The gait was wobbly with inward rotation of the feet. She complained of knee pain. Body height was 105.3 cm (-2.1 SD), body weight 16.5 kg (-1.4 SD), weight to height 35 percentile. Anthropometric examination revealed significant shortening of the limbs: Sitting height 64 cm (0.2 SD), subischial leg length 41.3 cm (-4 SD), arm span 94 cm, upper extremities 40.6 cm (-3,1 SD). Arm circumference was normal, 18.2 cm (0.1 SD), muscle hypotrophy in lower limbs was revealed: calf circumference 19 cm (-2.9 SD). Head circumference 49 cm (-1.3 SD).

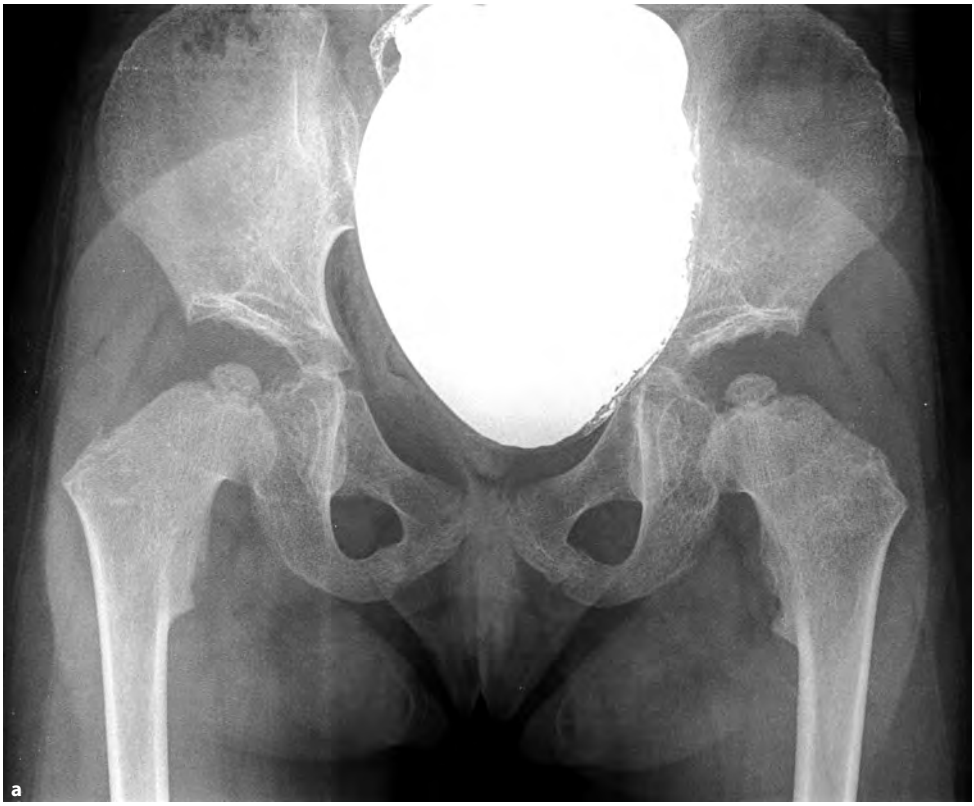
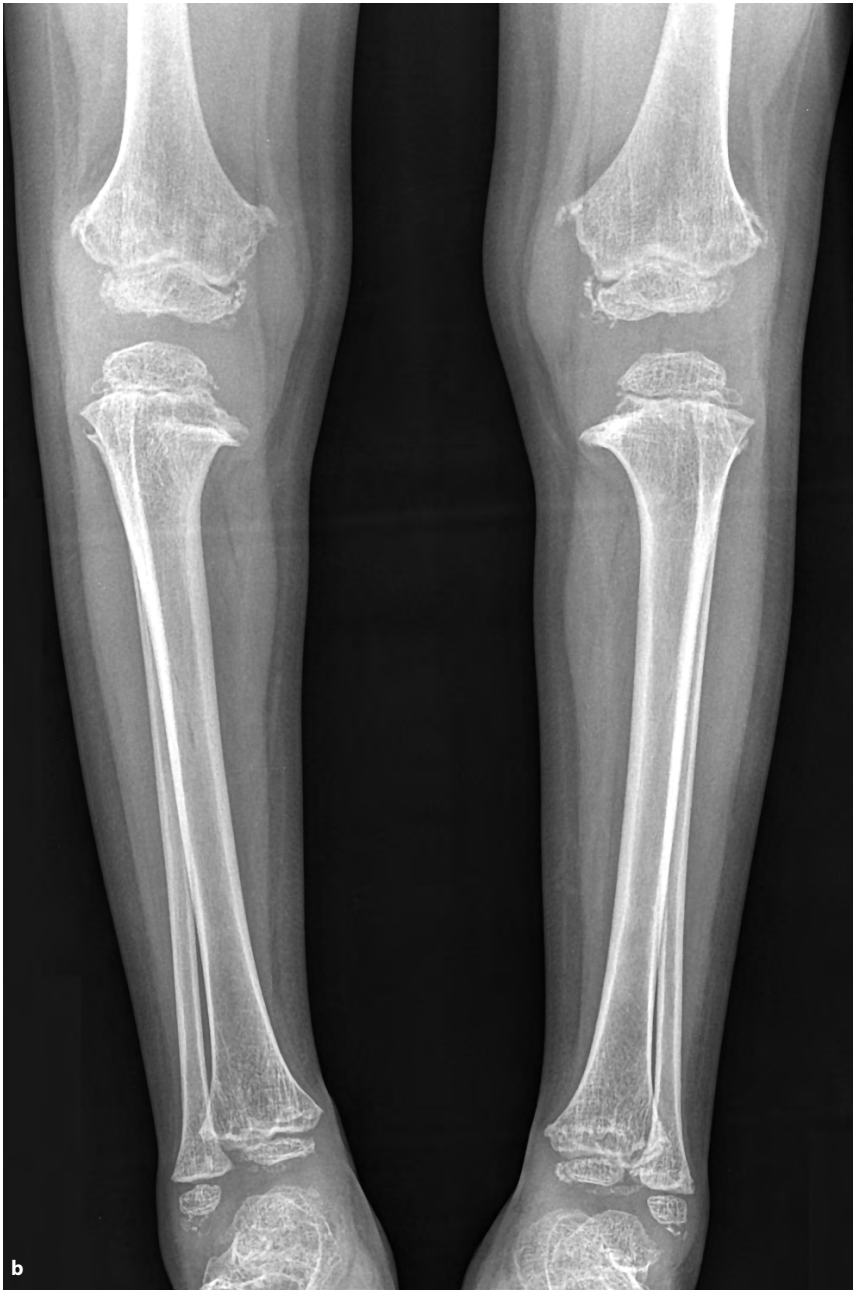


Figure 3 a–d. Case 1, X-rays at 5.5 years showed epiphyseal and metaphyseal dysplastic changes in the hip, knee and ankle joints. **a.** Note the small proximal femoral epiphyses, which have a rough surface. Distal femoral epiphyses are small with obvious fragments. **b.** Metaphyses in the knee joint region are abnormal with irregular margins. **c.** this image documents dorsolateral dislocation of the proximal end of the right tibia. **d**. X-ray of the left hand at 8 years of age showed an irregular appearance of the carpal bones, the tubular bones of the hand are slightly shortened and wide – see 1st metacarpal bone, small jagged epiphyses and dysplastic metaphyses, bone age is delayed (depicted X-rays are on following three pages).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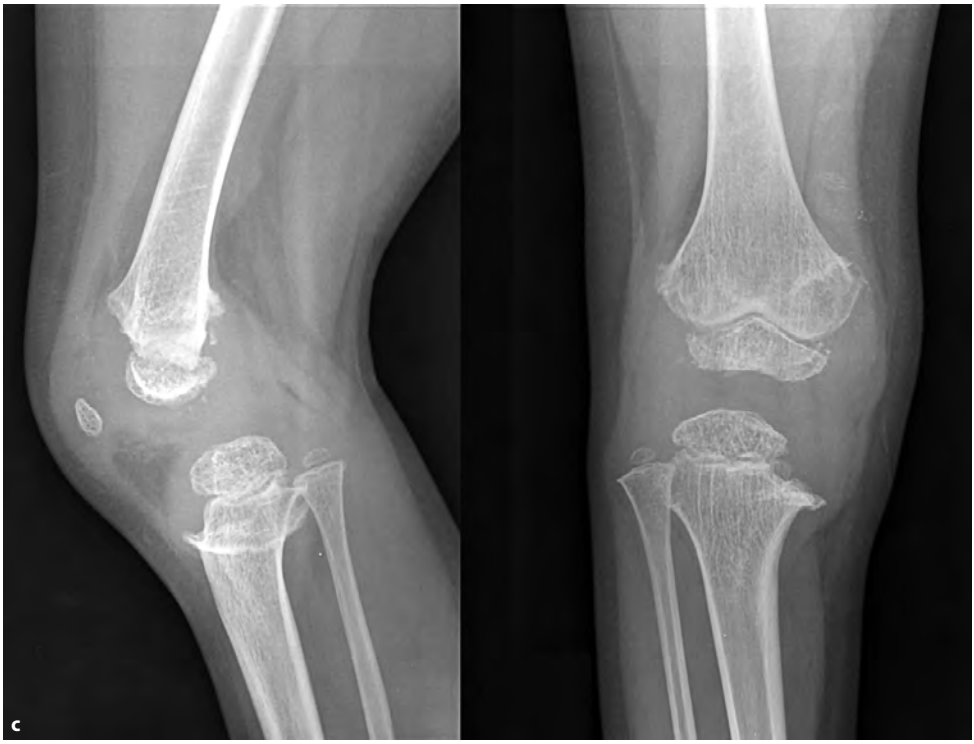
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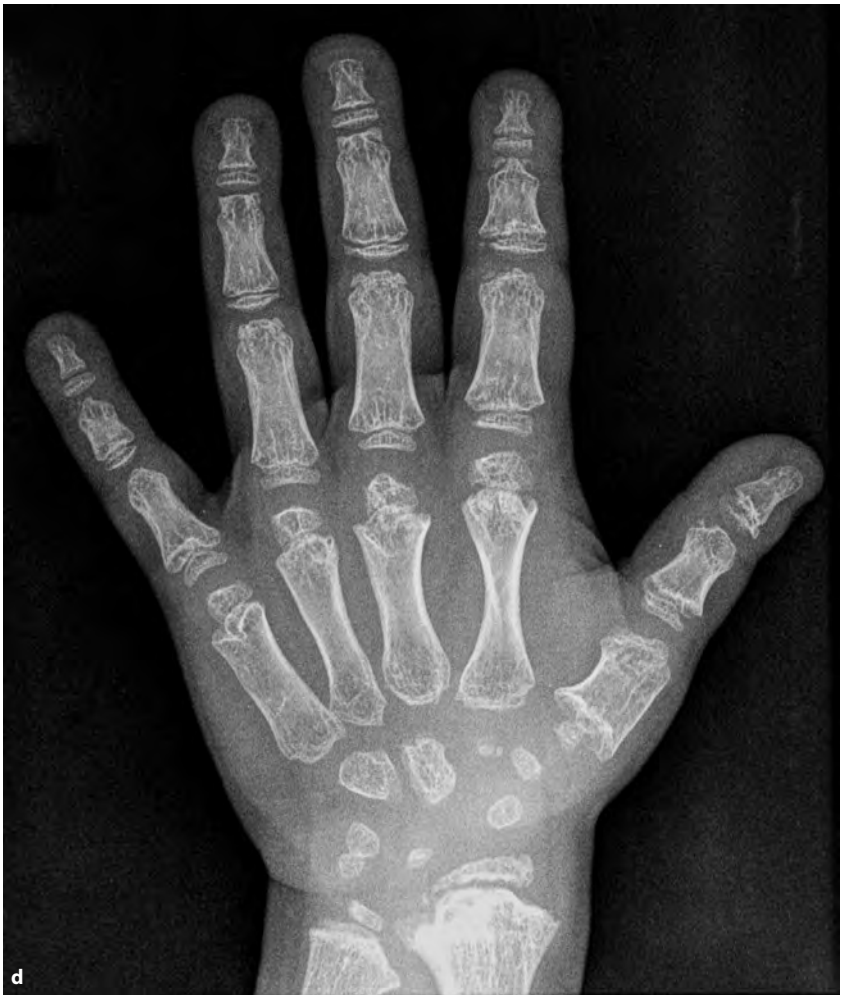


TREATMENT

Varosity of the right knee joint was initially treated with a brace with preload (**Figure 4 a, b**). After 9 years of age, the clinical condition worsened. The gait pattern deteriorated. She was able to walk 200 m. At 10 years of age, she started using a four-point knee orthosis for walking to ensure antero-posterior instability of the right knee joint (**Figure 4 c, d**). Flexion contractures of the elbows and hips, limitation of upper limb elevation and lumbosacral hyperlordosis became more pronounced. The radiological findings also worsened. X-ray of the knee joints at 11 years showed epimetaphyseal changes, varosity of the proximal metaphysis of the tibia – more to the right, and external luxation

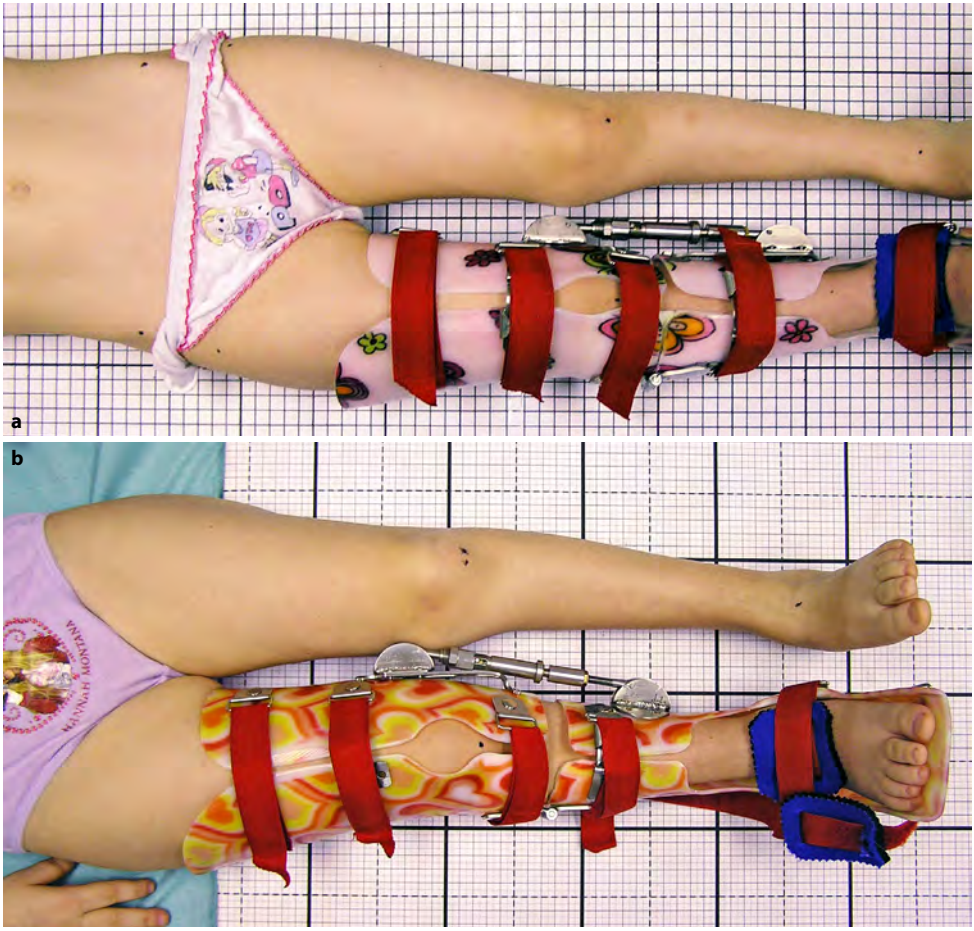


Figura 4 a–d. Case 1, treatment of varosity of the right knee using an orthosis with preload – **a, b**; **c, d**. four-point knee orthosis for walking to secure anteroposterior instability of the right knee joint. Pictures c, d – see next page.

of the patella bilaterally (**Figure 5 a)**. At the age of 11 years, a temporary external hemiepiphysiodesis of the tibia proximalis bilateralis (by eight-plates) was performed to correct proximal tibial varus. On the right side, the postoperative period was complicated by infection in the surgical wound. After two months the eight-plate had to be removed. A satisfactory effect was achieved on the left lower limb. The eighth plate was extracted at 12 and a half years of age (**Figure 5 b, c**). Despite of complex treatment (physiotherapy, orthoses, surgical treatment) the disease increasingly limited the patient's life activities. Due to knee pain, she walked only 70 meters, using a four-point orthosis with knee extension arrest on the right leg. She began using a wheelchair. A long-planned surgery –

c

d

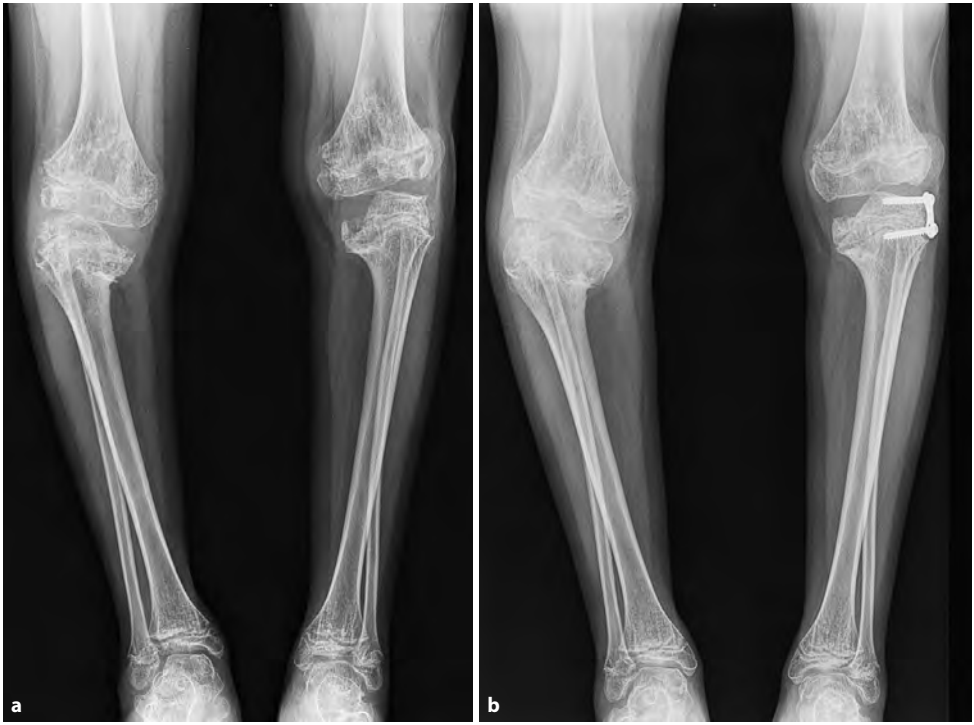
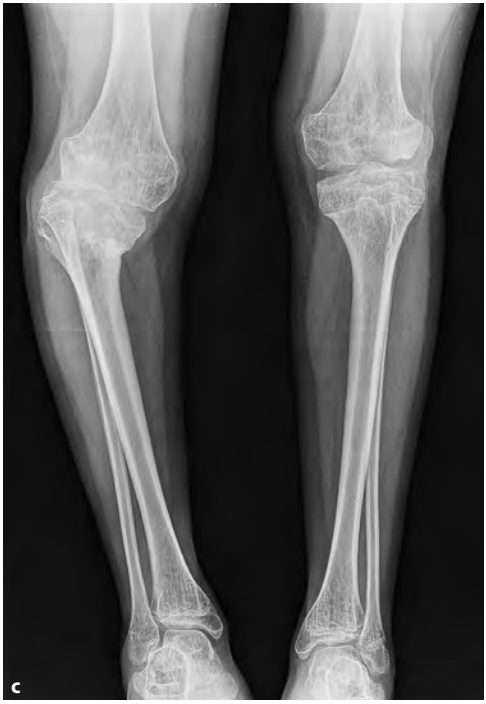


Figure 5 a–d: Case 1, **a.** X-ray of the knee joints at age 11 years showed, in addition to epimetaphyseal changes, varosity of the proximal metaphysis of the tibia – more to the right, and bilateral external luxation of the patella. **b.** two months after temporary external hemi-epiphysiodesis of the tibia proximalis bilateralis, the eight-plate on the right side had to be removed because of infection. **c.** the eight-plate from the left proximal tibia was extracted at 12.5 years, i.e. 18 months after surgery, when the tibiofemoral angle of the left knee joint was satisfactorily corrected. **d.** X-ray of the hip joints at the age of 13 years showed very short and varus femoral necks, flattened proximal femoral epiphyses, vertical position of dysplastic acetabula and subluxation of the hip joints. The greater trochanters are in the B position (see also next page).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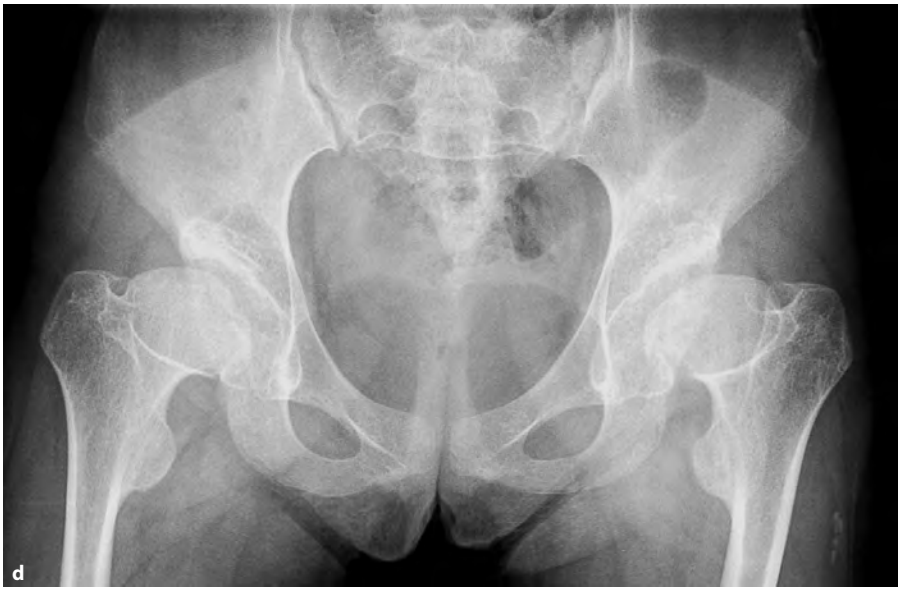
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corrective osteotomia of the proximal tibia was performed at the age of 17 years with a good result. Figures show the clinical findings and X ray features of the knee joints before (**Figures 6 a–d**) and after surgery (**Figures 7 a–d, 7 e–g**) .

CONCLUSIONS

Along with the gradual deterioration of the clinical condition, growth retardation became more pronounced from the age of 7 years. Although bone age was significantly delayed in the prepubertal period, puberty began at age 11 and proceeded relatively rapidly. At 11.5 years, bone age due to dysplastic changes was equivalent to that of a 13-year-old girl. The pubertal changes were not accompanied by any pubertal spurt; instead, growth retardation continued. Menarche was at 12.5 years.

The improvement of the lower limb axis due to complex treatment is illustrated in the **Figures 6a–c** and **7 a–d**. Both bilateral patella and dysplasia of the knee joint and subluxation of the dysplastic hip joints persist after growth has ceased. The patient walks unsupported at home and uses French canes outside. At present she studies at a private business school.

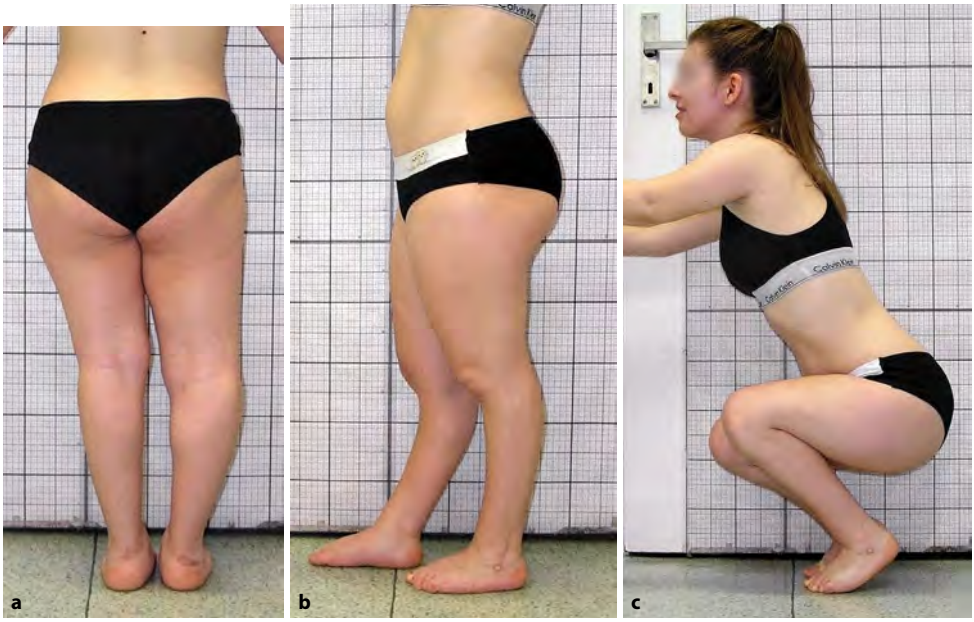


Figure 6 a–c. Case 1, 17 years old. Clinical findings before corrective osteotomy of the right tibia. Note the mild pelvic asymmetry, varosity and hyperextension of the right proximal tibia in standing and slight limitation of dorsal flexion at the ankle joints during squatting.

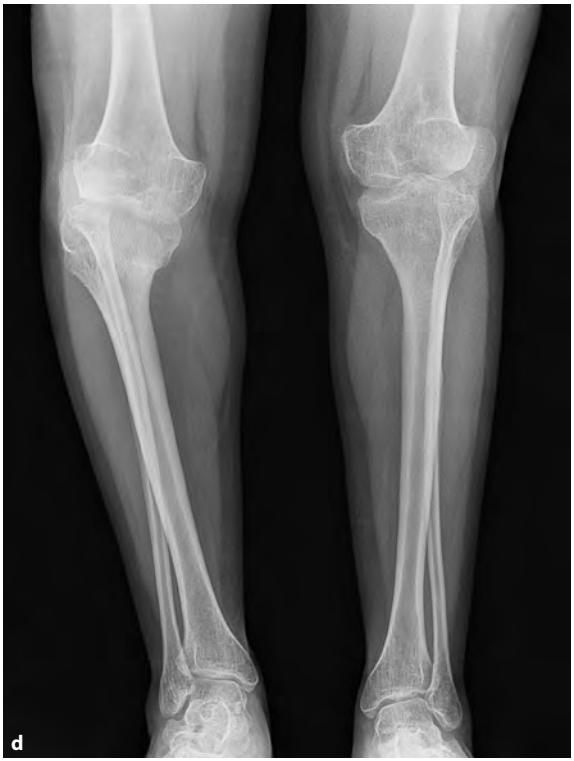


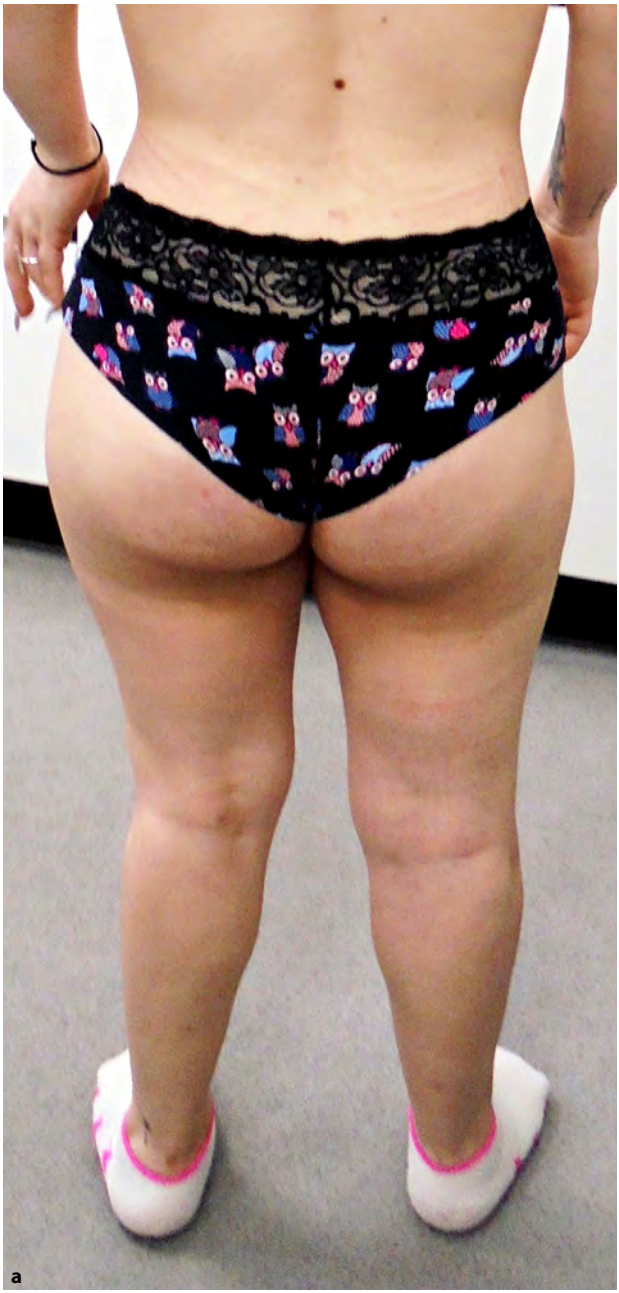
Figure 6 d. Preoperative radiographs – note the lateral dislocation of both patellae, the varosity and some lateral dislocation of the proximal end of the right tibia.

PROGNOSIS

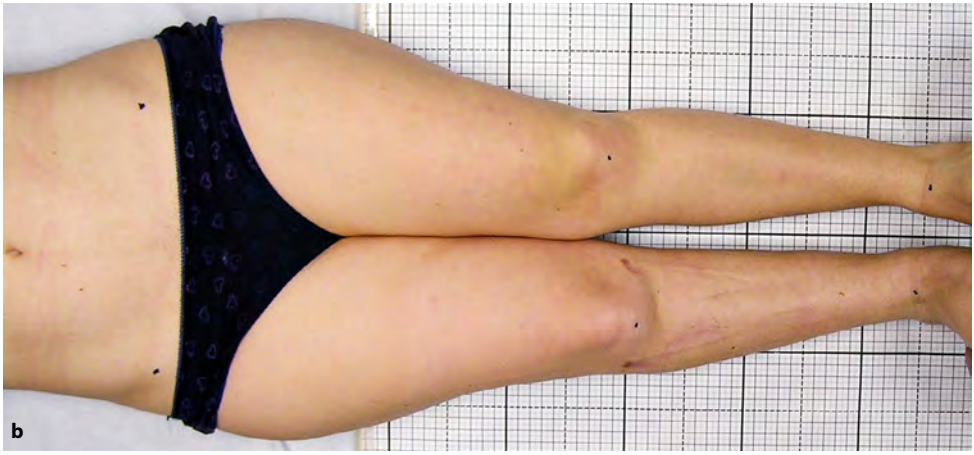
Prematurely developing osteoarthrosis of both hip and both knee joints will be presumably an indication for replacement with total endoprostheses in middle age.

Molecular genetic testing found an unpublished variant c.1450T>C in *COMP* gene in the heterozygous state leading to amino acid substitution p.Cys484Arg in the 7th calmodulin-like repetitive region. As this particular variant was not reported in literature, prediction programs were used for ascertaining pathogenicity. Applied software predictors assessing the potential effect of missense substitutions on protein function and structure agree on a pathogenic effect on the protein. This *COMP* gene variant is classified as probably pathogenic by the American College of Medical Genetics and Genomics. Sequence variant c.1450T>C was excluded in both healthy parents and thus supporting *de-novo* mutation and its pathogenicity in our patient.

Genetic testing was performed by massive parallel sequencing using Clinical exome panel followed by Sanger sequencing.



Figures 7 a–d: Case 1, 19 years, after surgery. Final height is 139.5 cm (-4.4 SD), weight 43.4 kg, BMI 22.3 (0,4 SD). Sitting height is normal 86.3 cm (-0.4 SD), subischial length 53.2 cm (-9.6 SD). Upper extremities are also short, arm span is 126.7 cm, measured segment by segment 129 cm. **a–d**. almost physiological tibiofemoral angle in standing and lying position, corrected internal tibial torsion on the right, slight internal torsion on the left, external luxation of the kneecap bilaterally during knee flexion (see also next page).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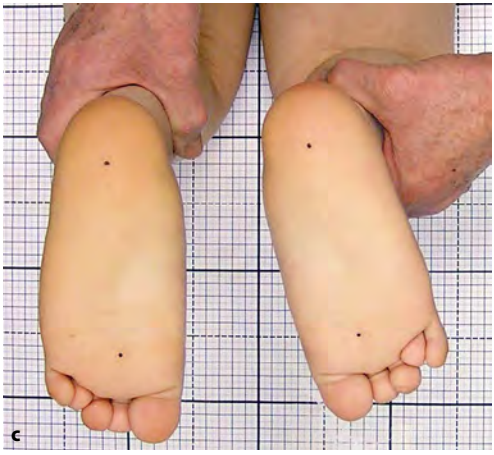
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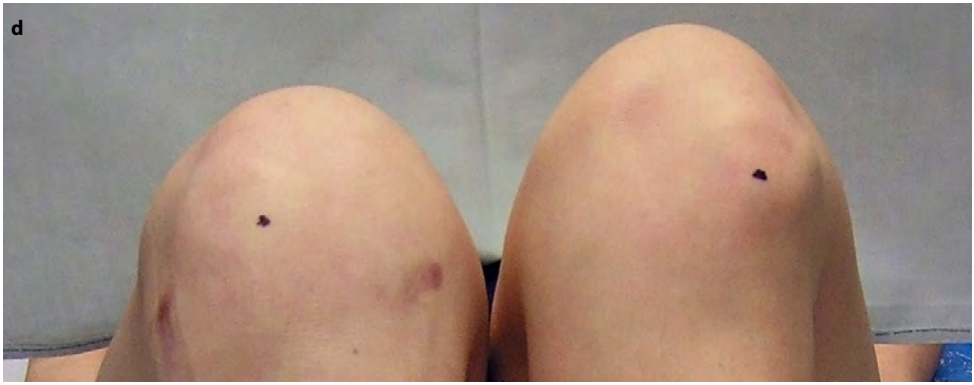
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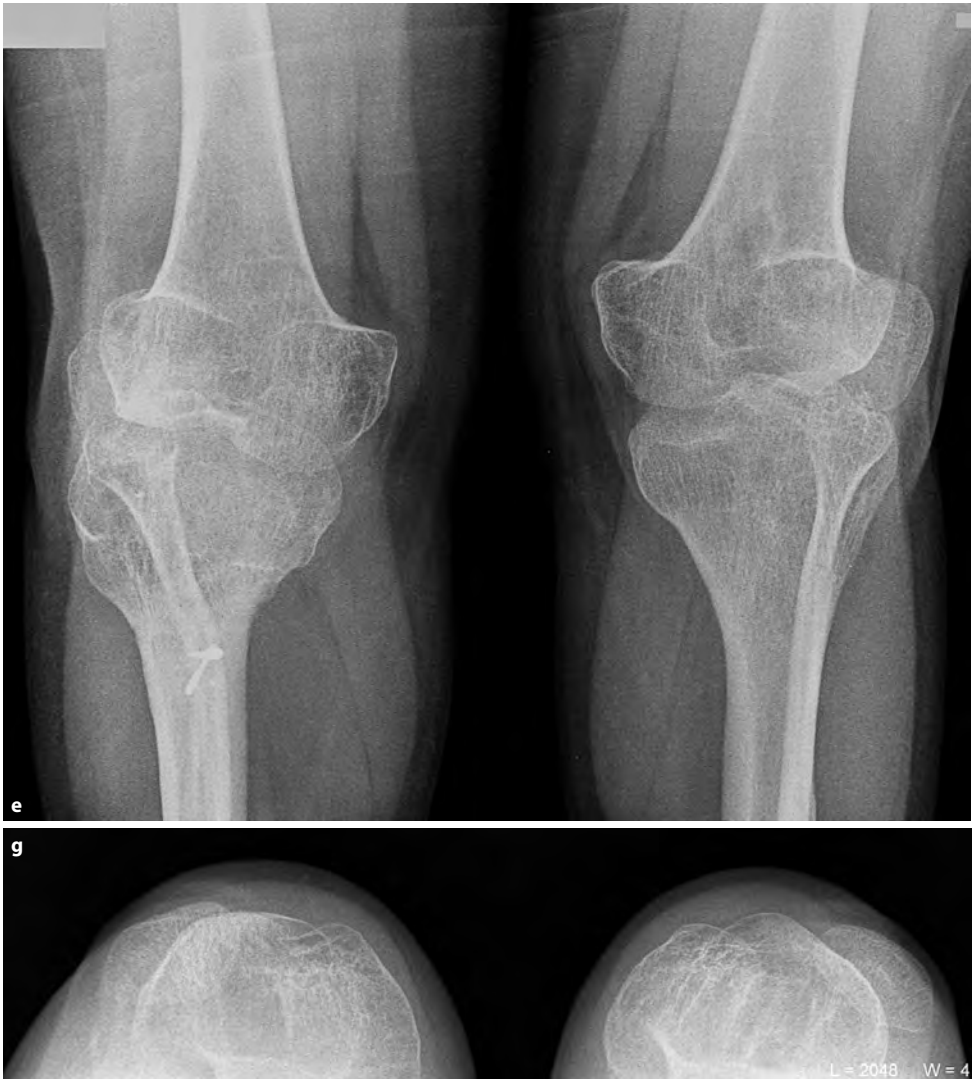
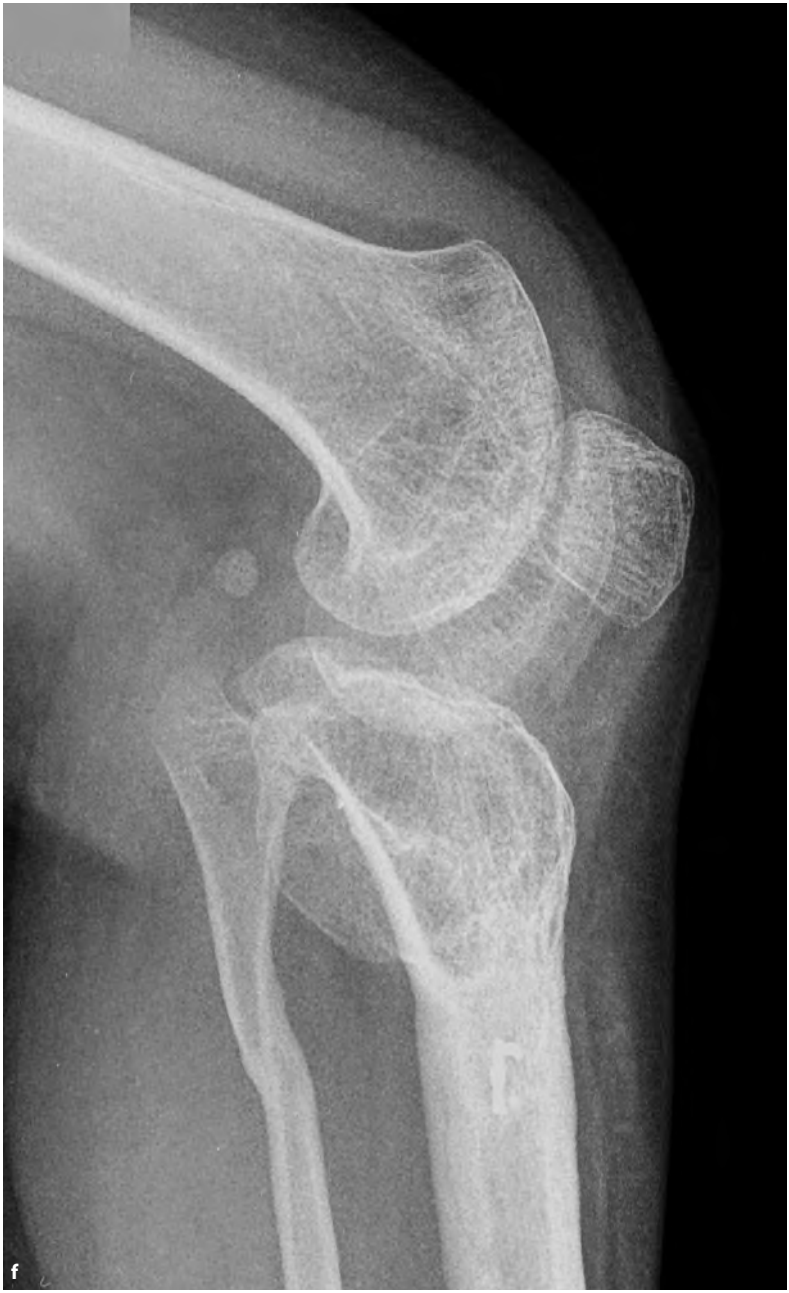


Figures 7 e–g. Case 1, 19 years, after surgery. Final height is 139.5 cm (-4.4 SD), weight 43.4 kg, BMI 22.3 (0.4 SD). Sitting height is normal 86.3 cm (-0.4 SD), subischial length 53.2 cm (-9.6 SD). Upper extremities are also short, arm span is 126.7 cm, measured segment by segment 129 cm. **e, f**. complete remodelling of the corrective osteotomy of the proximal tibia and fibula on the right. Slight external and posterior dislocation of the proximal tibia on the right persists. **e, g**. the AP and axial projection of the knees show well bilateral external luxation of the patella (X-ray f is on the next page).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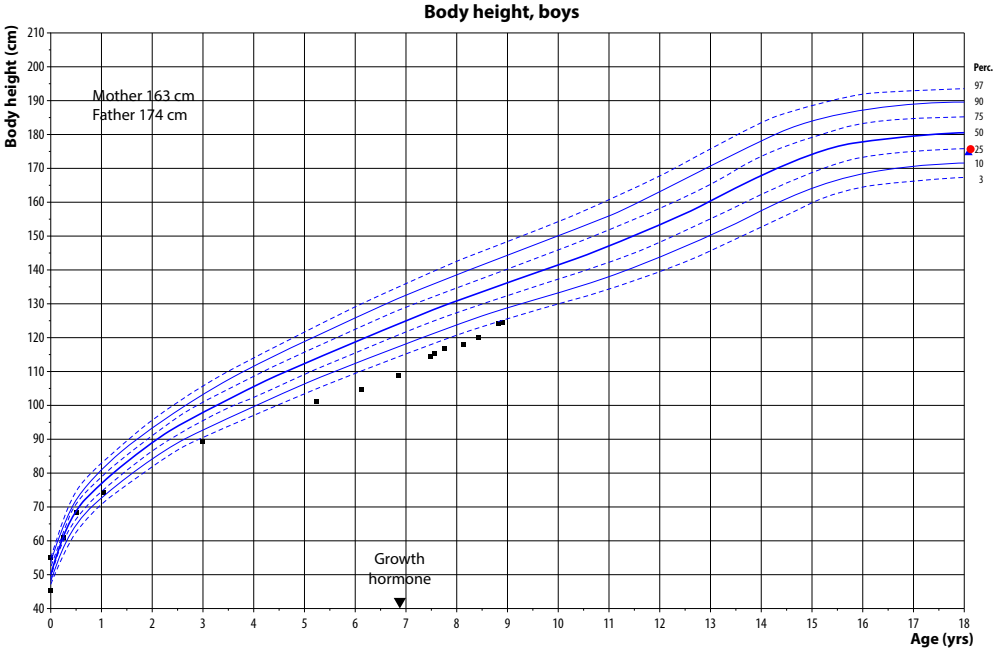
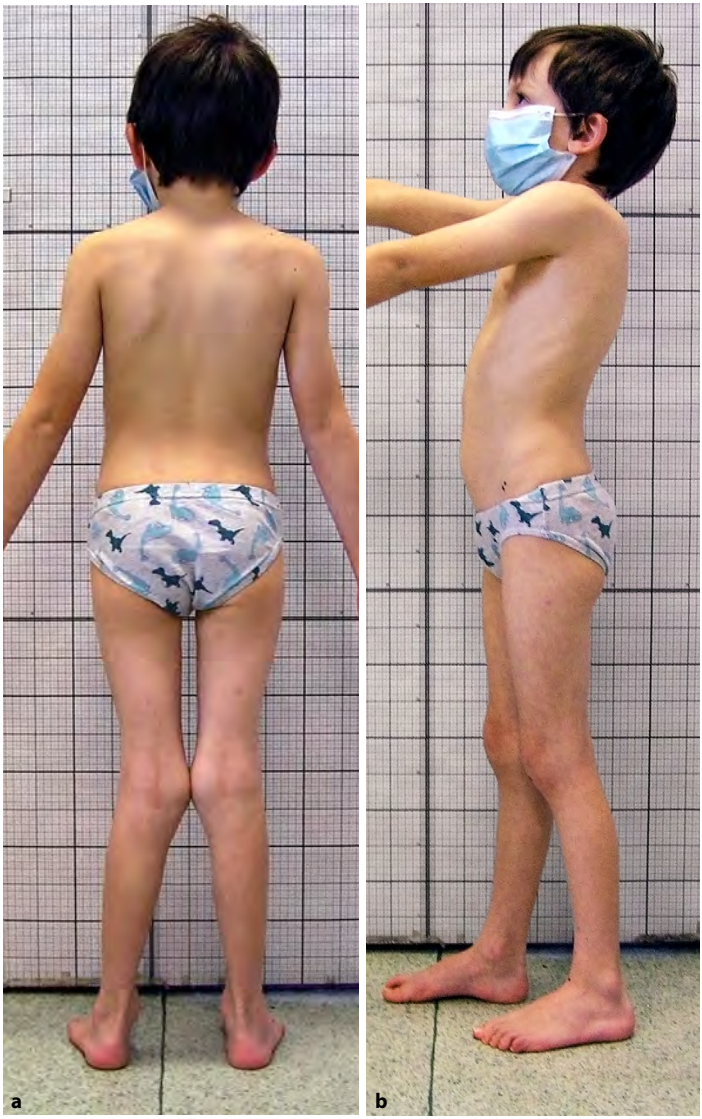
CASE 2

The boy was followed by an endocrinologist for growth failure (-3.1 SD) and autoimmune thyroiditis. He was referred to the Centre for Defects of Locomotor Apparatus (CDLA) for evaluation to refine the genetic diagnosis and to consider orthopaedic treatment for knee valgus. He was born at 38 weeks gestation, small for gestational age by body length (2670 g/45 cm). At the age of 6.1 years, he measured 104.5 cm (-3.1 SD). Anthropometric examination showed no disproportion. The clinical picture was unremarkable. However, the family history was interesting. His mother reportedly suffered from Perthes disease and underwent bilateral total hip replacement at the age of 37, her father at the ages of 40 and 60. We suspected dominant transfer collagenopathy II or other extracellular cartilage matrix disorders. The boy was referred for genetic testing. At the age of 6.9 years, growth hormone treatment was started for SGA/IUGR (small for gestational age/intrauterine growth retardation) with a favourable effect – growth rate in the first year of treatment was 8.7 cm/year (see **Graph 1**). *Genetic testing* using massive parallel sequencing revealed heterozygous variant c.437T>C (p.Leu146Pro) in the *MATN3* gene. Its presence was verified by direct Sanger sequencing. This variant is classified as a variant of uncertain significance in genetic database ClinVar. Applied software predictors assessing the potential effect of missense substitutions on protein function and structure



Graph 1. Case 2. Growth chart describes growth retardation by age 7 (-3.1 SD), when growth hormone treatment would have been initiated. Growth velocity in the first year of treatment was 8.7 cm/year, in the second year 7 cm/year. During the first two years of treatment SDS of body height increased to -2 SD.

agree on a pathogenic effect on the protein. The Human Gene Mutation Database (HGMD) database lists similar pathogenic sequence variant c.437T>**G** (p.Leu146Arg) associated with MED type 5 (**15**). According to OMIM, pathogenic sequence variants in the *MATN3* gene are associated with MED type 5. Variant c.437T>C was detected in patient's mother, who was subsequently diagnosed with MED, and thus supporting its pathogenicity in our patient.



Figures 8 a–h. Case 2, 8.2 years old boy: **a, b.** He measured 117.9 cm (-2.5 SD), body weight was 20.3 cm (-2.2 SD), and the weight-for-height ratio was at 24th percentile. A sitting height of 64.5 cm and an arm span of 121.5 cm indicated normal proportionality. Chest circumference was 58.9 cm (-0.8 SD), slightly above average for body height with an increased sagittal diameter, chest index 79.3 (1.6 SD). Accentuated lumbar lordosis due to hip flexion contractures and valgus in the knee joints became more pronounced.

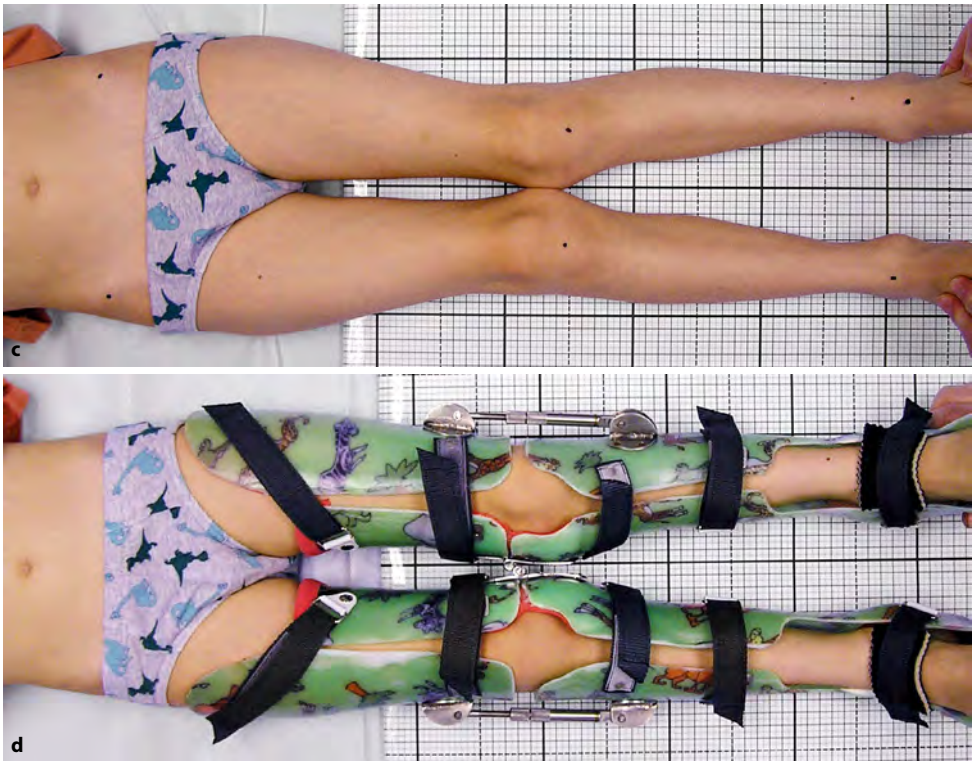
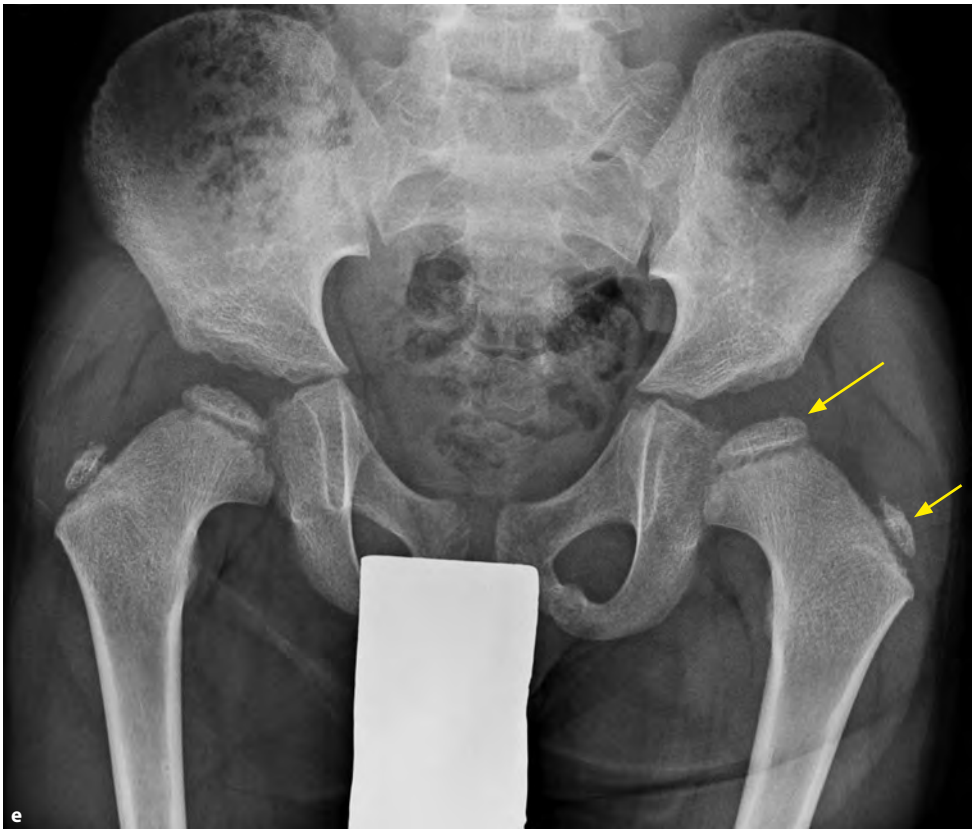


Figura 8 c, d. Case 2, 8.2 years old boy: **c, d**. knee joints valgosity and treatment using orthoses with preload.

Clinical and radiological examination of the index case was performed in the CDLA at the age of 7.5 and 8.2 years. With growth, posture gradually deteriorated – see **Figure 8 a, b**. X-rays showed dysplastic epiphyseal changes of long bones and a mild of spine – see **Figure 8 e–h**. Clinical and radiological findings were consistent with MED type 5.

Knee valgus was progressing. Tibiofemoral angle was about 15 degrees bilaterally, intermalleolar distance was 8.4 cm. That is why the orthotic treatment was started in the night mode – see **Figure 8 c, d.** Growth hormone treatment continues. Growth velocity in the second year was 7 cm per year. During treatment, the limbs grew faster than the trunk.

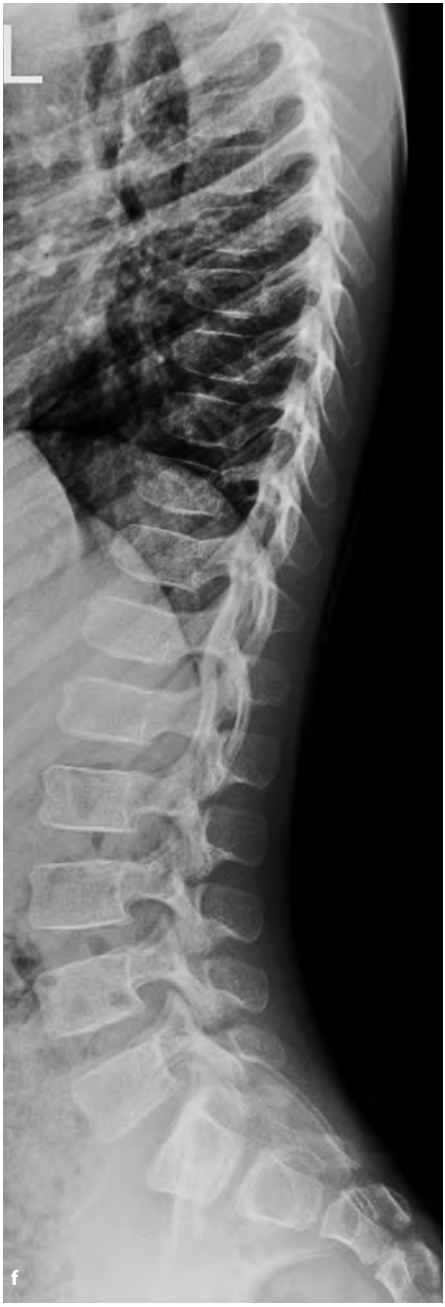
Younger sister was examined at the age of 6 years with conclusion: familial short stature 105 cm (-2.6 SD) affected by hypothyreosis and coeliac disease. However, even with adherence to a gluten-free diet, there was no catch-up growth. Radiological screening of skeleton performed epiphyseal dysplastic changes of hips, knees, hands and vertebral bodies of thoracic spine which correspond to the diagnosis of MED. Diagnosis was verified by molecular testing as in brother and mother.



Figures 8 a–h. Case 2, 8.2 years old boy: **e–h**. X-rays of hips and pelvis, spine in lateral projection, knees and tibias and left hand in AP projection and at the age of 7.5 years showed. **e**. small flat epiphyses of femoral heads, small ossification centres of great trochanters. **f**. accentuated lumbosacral lordosis, platyspondyly in the thoracic and lumbar region. **g**. valgus knees, small, flattened epiphyses of distal femur, proximal tibia, and fibula bilaterally (see arrows), widened and thickened metaphyseal margins of distal femur and proximal tibia bilaterally (see arrows) and vertical bands of thickened bone structure in metaphyses. **h**. pseudoepiphysis of the 1st and 2nd metacarpal (see arrows – 2), double ossification centres of the head of the 2nd–5th metacarpal (see arrows – 1).

Conclusions

On the basis of radio-clinical examination and genetic testing we confirmed the diagnosis of MED, type 5 in case 2 and also in his mother and sister. We assume the same diagnosis in the younger sister. If treatment of bilateral valgus knee with preloaded orthoses is not successful, transient hemi-epiphysiodesis with eight plates will be indicated.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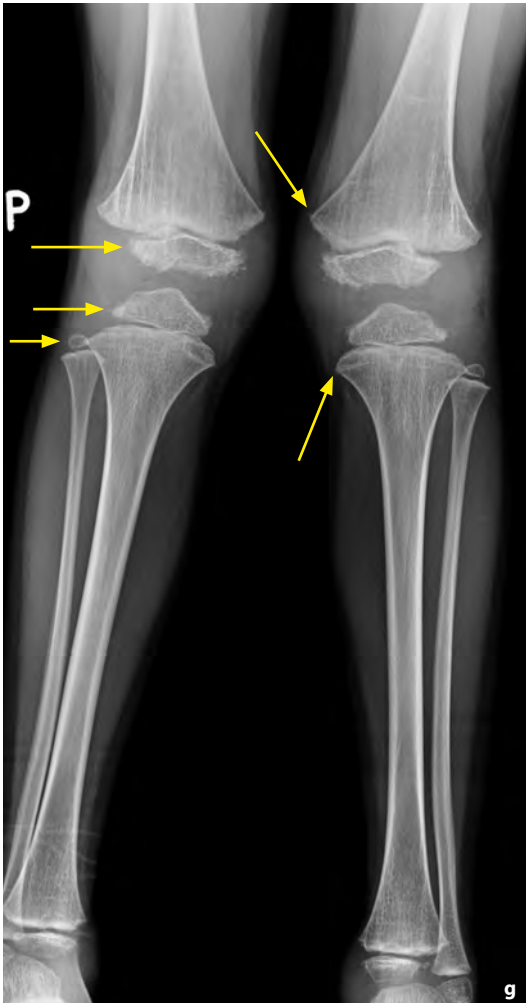
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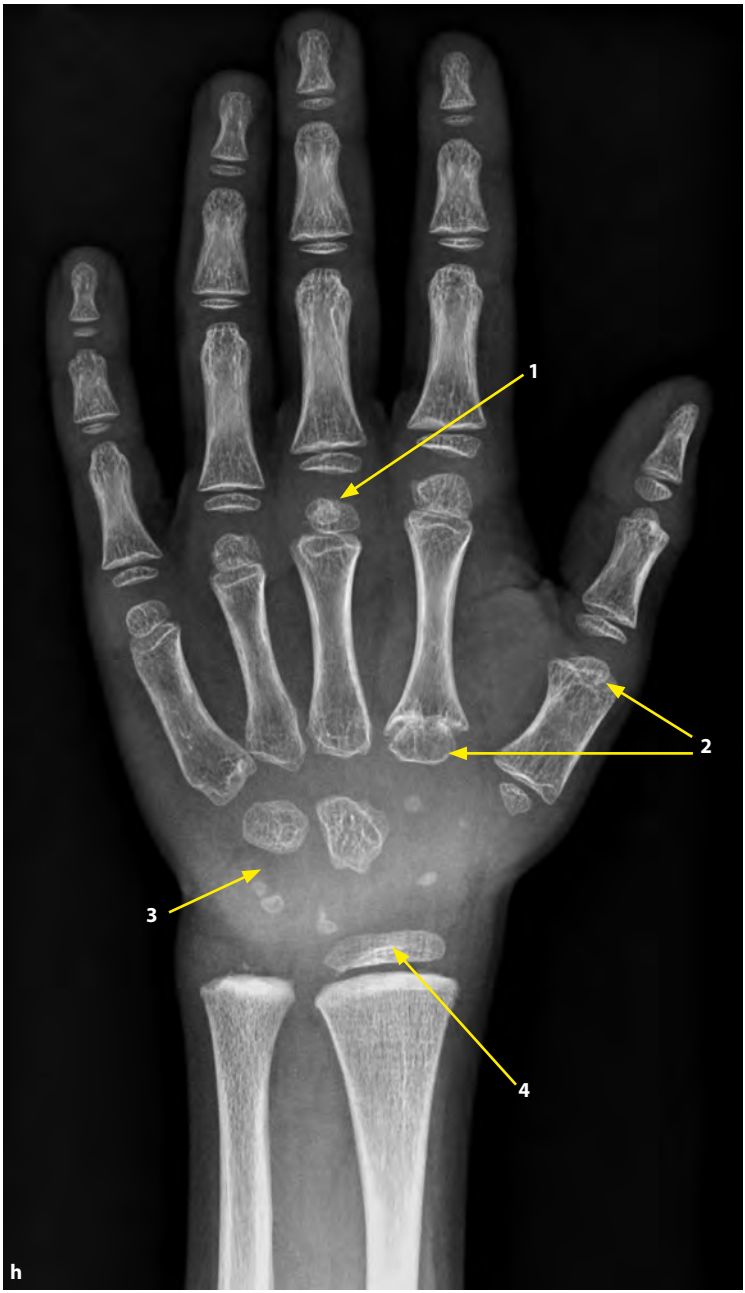
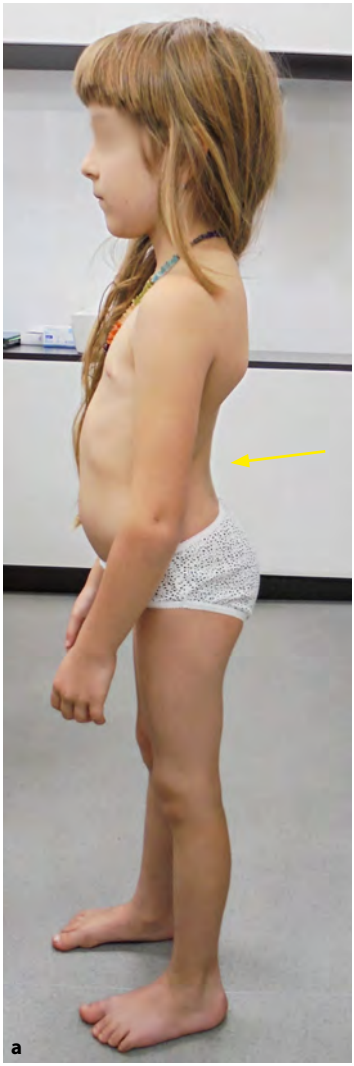


1 – double ossification centres of the head of the 2nd–5th metacarpal
2 – pseudoeiphyses
3 – delayed ossification
4 – flat epiphysis

CASE 3 (2 siblings)

A 6 years and 10 months old girl, daughter of healthy parents, was referred to CDLA for right hip pain. Preventive hip examination in early infancy was not done. Independent walking at 21 months. **Clinical examination** revealed genua valga, hypotrophic thigh muscles, hip flexion contracture especially on the right and lumbar hyperlordosis (see arrow) – see **Figure 9 a, b**.



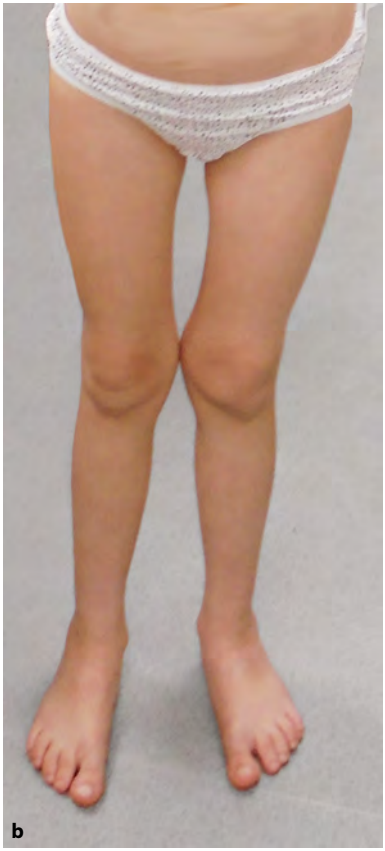
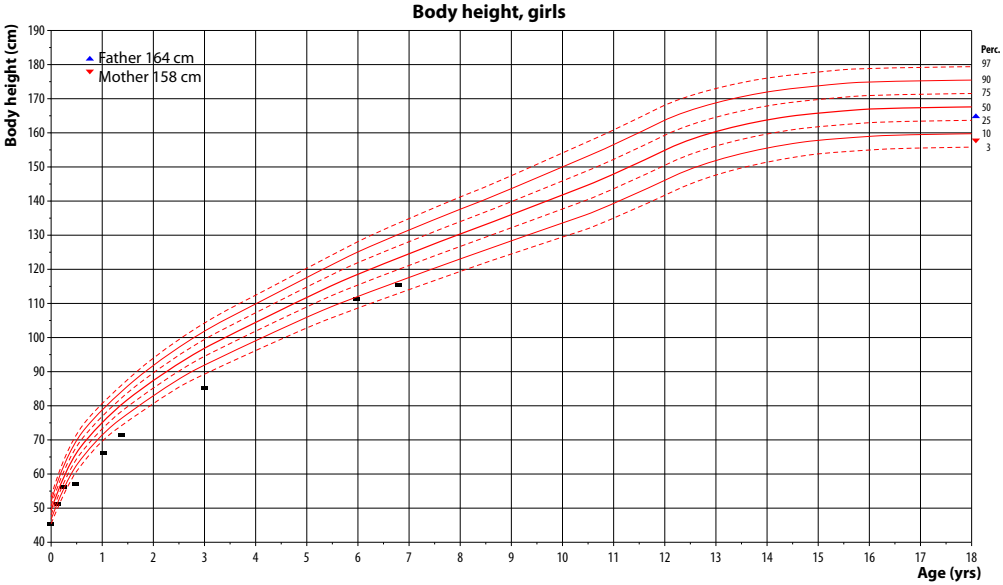


Figure 9 a–e. Case 3: 6 years and 10 months old girl. **a, b**. Clinical findings; **c, d.** radiographs of the hips and left knee joint: Varous wide and short femoral necks (collodiaphyseal angle 110°), flattened see arrow at c, the greater trochanters in the B position and small dislocated double layered patella of the left knee see arrows at d. **e.** X ray of hips of 21-month-old brother: wide steep acetabulum – on the right side, proximal femoral epiphyses not yet ossified – arrow on the left side.



Graph 2. growth curve of case 3 demonstrates small growth of prenatal origin.

Laboratory examination showed negative markers of inflammation. **Ultrasound examination** showed coxitis.

Anthropological examination showed growth failure of prenatal origin – see **Graph 2**. Birth weight in the 37th week of gestation was 3000 g, length 42 cm (small for date). Body height at the age of 6 years was 115,1 cm (-1.5 SD), weight 19,6 kg, BMI 14,8 (-0,4 SD). Sitting height 61 cm (-1,1 SD) shows rather shorter trunk, chest is flat.

Radiological features were clearly suggestive of MED – see **Figure 9 c, d**.

Her younger **21-month-old brother** was also born small for his age (3000 g, 42 cm at 37 weeks). He had a more pronounced growth failure of 75.5 cm (-3 SD) with short limbs. **Radiological examination** at this age showed a wide acetabulum. The proximal femoral epiphyses were not yet ossified – see **Figure 9 e**.

Their **4-year-old sister** was healthy with no clinical or radiological signs of bone dysplasia.

Genetic testing revealed a homozygous pathogenic variant c.1957T>A (p.Cys653Ser) in the *SLC26A2 g*ene, which is associated with recessive MED type 4. The c.1957T>A variant has already been described in the literature and is classified as pathogenic in genetic databases. This variant is one of the most frequently found pathogenic variants of *SLC26A2* and has been described in

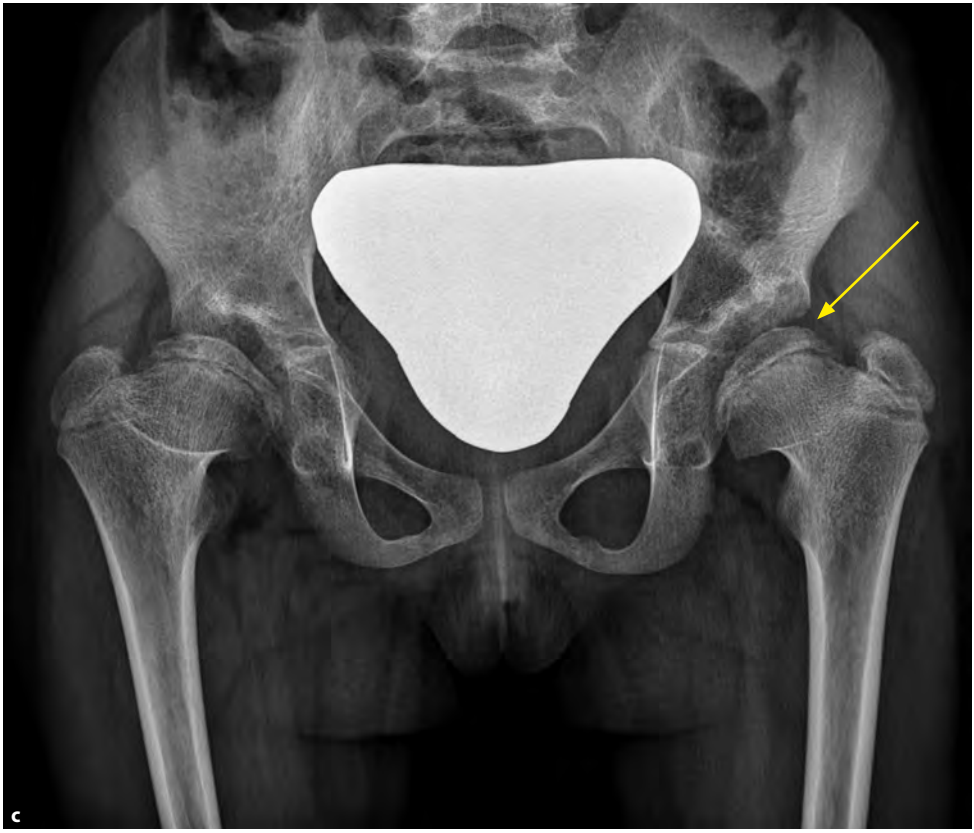


Figure 9 c: Case 3.

homozygous and compound heterozygous states in individuals with recessive MED type 4 and diastrophic dysplasia. Genetic testing was performed by massively parallel sequencing using a clinical exome panel followed by Sanger sequencing. Both parents are healthy carriers of one copy of the pathogenic variant.

CONCLUSIONS

Based on clinical and radiological findings and genetic testing, the patient and her brother were diagnosed with **MED type 4**. Genetic testing is also planned for a 4-year-old sister with no radioclinical signs of bone dysplasia.

Further comprehensive treatment and follow-up of both affected siblings will be due to the family's relocation to another ward.

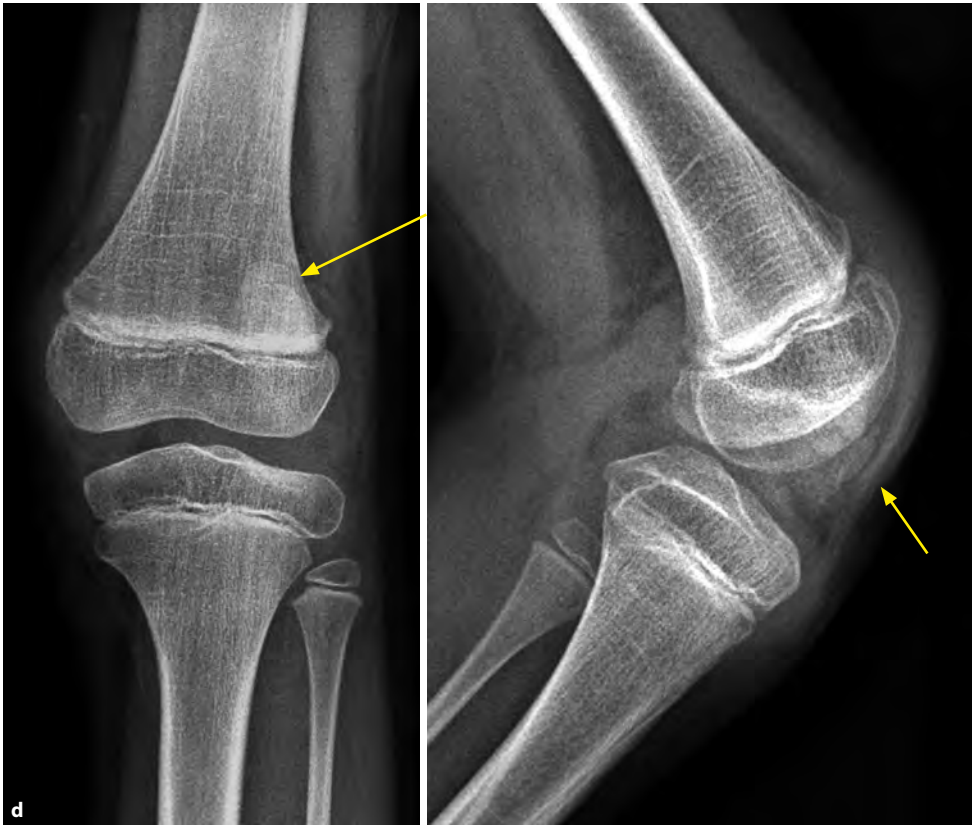


Figure 9 d: Case 3.

DISCUSSION

According to Spranger et al. (**35**), Ribbing's disease (**31**) is a mild form of MED with flat epiphyses in infancy and mild involvement of the bones of the hand, which differs from the severe Fairbank form (**8**) with small epiphyses and late ossifying irregular carpal bones and more pronounced changes of the metacarpals and phalanges. MED is a genetically heterogeneous bone dysplasia with a variable course.

At present, seven genes are known to cause MEDs. Their common denominator is the defective formation of ECM cartilage and disturbation of its integrity. Pathological changes in these genes lead to a decrease in articular cartilage quality and affect endochondral ossification to varying degrees. The radiological findings are dominated by epiphyseal changes, but as the differentiation and survival of chondrocytes is affected to varying degrees, metaphyseal changes also occur. The most common cause of the AD form of MED is mutation in the *COMP* gene. Our case 1 with

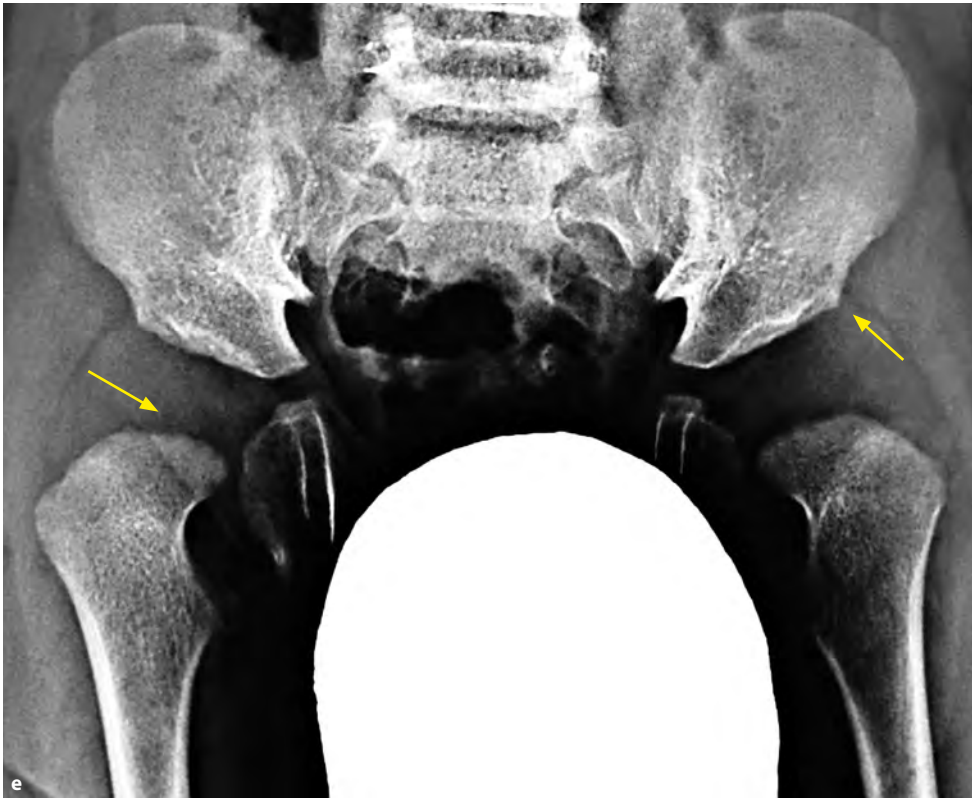


Figure 9 e: Brother of the case 3: 21 months

c.1450T>**C variant** is an example. Similar variant c.1450T>**G** has been described in the literature in a patient with PSACH (**19**). Pathogenic variants in the *COMP* gene are associated with PSACH and MED and there is a phenotypic continuum between both dysplasias. Although Mabuchi at al diagnosed patient with c.1450T>**G** variant with PSACH, clinical and radiological findings in our patient do not meet PSACH criteria and are suggestive of MED type 1. Mutations in *COMP* produce clinical various phenotypes ranging from early onset arthritis (**32**) through above-described MED to the severe PSACH, which is characterized by marked short stature (105–128 cm), deformity of the legs, ligamentous laxity (**6, 12, 16**) and significant spinal disability.

Since the 1990s, more than 40 novel mutations in *COMP* have been identified (**34**); however, genotype-phenotype correlation is not yet fully understood. It is hypothesized that PSACH and MED mutations variably affect the cellular trafficking behaviour of COMP and that the extent of defective trafficking correlates with clinical phenotype (**12**). Liang et al (**18**) analysed genotype and pheno-

type in 14 patients with *COMP* mutations (12 with PSACH, 2 with MED) and 25 controls. In addition to the determination of *COMP* variants, clinical description, radiology scoring system and anthropometric parameters, median serum COMP levels were determined. Height Z-scores and serum COMP levels were significantly lower in patients carrying mutations located in calmodulin-like domains 6, 7, and 8. As the two phenotypes overlap to different degrees, PSACH and MED are suggested to combine to produce "spondyloepiphyseal dysplasia, COMP type".

However, case 1 with its height of 139.5 cm and clinical course, it represents the most severe case of MED among our patients. Severe short stature in our patient could be explained by the fact, that both above mentioned *COMP* variants are located in the 7th calmoduline-like repeat region (CLR) that is associated with severe phenotype according to the literature (**19**). Patients diagnosed with PSACH have *COMP* mutations located in the 7th CLR particularly in the five-aspartates repeats (469–473) resulting in extremely severe short stature. However, our patient has its mutation in different five-aspartates repeat position (484) and thus leading in phenotype harbouring PSACH and MED. Our result is also consistent with the findings of Seo et al 14 (**33**). They showed on the basis of analysis of 59 patients that clinical manifestations of MED caused by *MATN3* were milder than manifestations of the *COMP* mutation group.

Otherwise, the clinical and radiological findings of our patients were similar. Our case 2 with MED type 5 (pathological variant of *MATN3*) showed certain vertebral and metaphyseal changes.

Recessive MED (type 4) is caused by mutations in the *SLC26A2* gene. This gene is also known as the diastrophic dysplasia sulfate transport or *DTDST* gene because its mutations also cause diastrophic dysplasia. In addition to the symptoms common to all MEDs, additional features reminiscent of diastrophic dysplasia are described in the literature: club foot, cleft palate, clinodactyly, or ear swelling. In our case, we only observed double layer patella which was not present in AD MED (**3**).

Treatment is symptomatic, including physiotherapy, orthotic and surgical treatment. Delayed ossification of the femoral heads and hip dysplasia is often an indication for abduction treatment in infancy (**26**).

In preschool age, varus or valgus deformities of the knee joints can be addressed with bending preload orthoses (**21**). Later, the method of surgical treatment is temporal hemi-epihysiodesis of the distal femoral or proximal tibial physis. After growth is completed, corrective ostetomies are individually indicated. Hip and knee replacements are considered between the ages of 30–50. Planning the timing of hemi-epiphysiodesis is complicated by the uncertain prognosis of remaining long bone growth. Despite the initial delay in ossification, growth plates may prematurely disappear in some patients. In our **case 1**, lower limb growth was terminated at the onset of puberty. Therefore, we recommend temporary rather than drilling (permanent) hemi-epiphysiodesis at a younger age for this diagnosis.

Growth hormone is not indicated for MED treatment. In our **case 2**, growth hormone therapy was initiated for the indication of IUGR/SGA before the diagnosis of MED. It was not interrupted because

of the favourable growth velocity. Literature data on growth hormone treatment of bone dysplasias is limited and the results are inconclusive (**9, 37**). Although our results in case 2 are promising so far, the actual effect of growth hormone treatment can only be assessed after the final height has been reached.

CONCLUSION

The authors present their experience with clinical, radiological and molecular genetic diagnosis of MED types 1, 4 and 5.

MED is generalized skeletal dysplasia associated with waddling gait and short stature, joint pains and contractures (progressing with age), lumbar hyperlordosis, knee valgosity and often dislocation of knee caps, joints deterioration (due to premature osteoarthritis, spondylosis and spondylarthritis).

At present, the eponyms Fairbank and Ribbing disease were abandoned in favour of molecular classification and designation of mild or severe symptoms.

MED is caused by pathogenic variants of genes encoding proteins involved in formation of cartilage extracellular matrix and its integrity: *SLC26A2, CANT1* (AR), *COMP*, *MATN3*, *COL9A1*, *COL9A2*, *COL9A3* (AD). The clinical and radiological findings are similar, but there is a considerable variability in the severity of the disease. Depending on the severity and localization of the predominant dysplastic ossification of the epiphyses of the hands, hips and knees in the X-ray image during growth, we can distinguish dominant MED type1 (caused by mutations in *COMP*), dominant MED types 2, 3, 6 (caused by mutations in *COL9A2, COL9A3* and *COL9A1*), dominant MED type 5 (caused by mutation in *MATN3*) or recessive MED type 4 and 7 (mutations in *SLC26A2*, *CANT1*). Factors influencing the clinical course are not completely understood.

MED is a relatively common skeletal dysplasia (AD 1:10000, AR 1:20000) (Medline, NORD). Dominant MEDs are more common than recessive ones. However, we judge that the actual incidence is even higher. Some patients are probably hiding under diagnoses familial short stature, premature osteoarthritis, knee valgosity/varosity, dysplasia epiphysealis capitis femoris (Meyer dysplasia), knee valgosity/varosity (see differential diagnosis).

Message to colleagues

We call on paediatricians and paediatric endocrinologists, as well as orthopaedic surgeons, orthopaedic prosthetists and physiotherapists to diagnose early postural disorders, spinal and thoracic deformities and abnormal gait patterns in congenital growth disorders and for suspicion on genetic skeletal diseases sent for specialized orthopedic-anthropological, genetic and molecular genetic examinations.

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ČASNÁ MOLEKULÁRNĚ GENETICKÁ DIAGNOSTIKA SPONDYLOMETAPHYSEÁLNÍ DYSPLAZIE – TYP KOZLOWSKI

EARLY MOLECULAR GENETIC DIAGNOSIS OF SPONDYLO-METAPHYSEAL DYSPLASIA – KOZLOWSKI TYP

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ABSTRACT

The article describes two cases – a 21.5-year-old patient and his 22-month-old daughter, in whom the diagnosis of Spondylometaphyseal dysplasia, Kozlowski type (SMDK) was confirmed by molecular genetic analysis using classical sequencing of the *TRPV4* gene, which revealed a heterozygous mutation c.1781G>A – (p.Arg594His) in exon 11 of the *TRPV4* gene. SMDK also affects the father and three brothers of CASE 1, who were diagnosed in 2006 by clinical and radiological examination.

Keywords – spondylo-metaphyseal dysplasia – Kozlowski type, platyspondyly, metaphyses, short trunk dwarfism, molecular genetic diagnostics, *TRPV4* gene mutation.

BACKGROUND

Spondylometaphyseal dysplasia – Kozlowski type (SMDK) is a very rare autosomal dominant disease but the most frequent form among spondometaphyseal dysplasias. K. Kozlowski, P. Maroteaux and J. Spranger et al. described the first case of Spondylometaphyseal Dysplasia, Kozlowski type in 1967 (**5**). Since that time many other cases with different severity of spine and metaphyseal skeletal changes were published (**6, 8, 13**). It is caused by the Transient Receptor Potential Cation Channel Subfamily V Member 4 (*TRPV4*) gene mutation (**2**). The major **clinical findings** are short-trunk type of dwarfism (anthropometric verification after one year of age). In early childhood we observe waddling gait – around 2 years of age, restricted joint mobility, occasionally genua valga, progressive kyphoscoliosis with thoracic deformity manifesting from 2nd to 3rd year of age, frequent

in adolescence and adulthood. The patients usually reach a height of about 130–150 cm, the intellect is intact and there is no distinctive craniofacial stigma. The major **radiographic features** are generalized platyspondyly (a radiographic sign of vertebral body narrowing) with characteristic anterior wedging of the vertebral bodies, irregular metaphyseal ossification with widening of the metaphysis, especially in the proximal femora where coxa vara is common and retarded bone age. Broad and short basilar portion of the iliac bones and horizontal acetabular roofs are presented in children. Furthermore, there is a kyphoscoliosis, which typically starts at the thoracolumbar junction, and pectus carinatum. All these radiographic features are not present at birth but develop in the first few years of life. They disappear – apart from platyspondyly – in adulthood. Therefore, the diagnosis of SMDK can be only suspected in adults (**1, 7, 8, 10, 11, 12**).

Until recently, the disease was diagnosed only on the basis of radiological and clinical findings. At present, the possibility of molecular genetic testing of SMDs is available. These methods can confirm the diagnosis with high reliability regardless the age of the patient. Molecular genetic testing is done in specialized centres, using either the classic sequencing or the Next Generation Sequencing (NGS) method. In case of a positive result, an examination of the other members of the family is recommended, and eventually the option of preimplant diagnosis is offered. The exact diagnosis is important as it predicts the clinical course and prognosis of the disorder. Treatment is symptomatic (**9, 14**).

The aim of this case report is to present an early molecular genetic diagnosis in a 22-month-old daughter of a Gypsy father with a radioclinical diagnosis of SMDK, which was made at 5.5 years of age and confirmed by molecular genetic analysis at 22 years of age.

CASES

CASE I: is a 21.5-year-old male patient of Roma origin, who was diagnosed with SMDK based on family history and the radiological signs of the disease at 5.5 years of age. At that time, he was 97 cm high (-3 SD), he had a disproportionate shortening of the trunk and a ventrodorsal enlargement of the thorax. Radiographs showed the typical markers, such as generalized platyspondyly with anterior wedging, metaphyseal changes caused by irregular metaphyseal ossification, broad and short basilar portions of the iliac bones, horizontal acetabular roofs, short femoral necks with severely dysplastic proximal femoral metaphyses and delayed bone age. At 13 years of age, he was diagnosed with morbus Osgood-Schlatter on both knees and premature osteoarthritis of the shoulder, knee joints and spondylarthritis (see **Figure 1 a–e)**. Currently, as an adult, the patient is 141 centimetres high (-5.6 SD), weight 51 kg (-2,4 SD), BMI 25,8 (1,4 SD), noticeable shortening of the trunk, severe fixed kyphoscoliosis and lordoscoliosis and disproportionality of the figure (sitting height 66 cm , i.e, -8 SD), arm span 169 cm (119.9% of body height). Ventrodorsal extension of the thorax and pectus carinatum was treated with a brace from 7 to 16 years in the night mode. Apparently, inconsistent corset therapy did not prevent progression of the chest deformity (see **Figure 2 a–d**). Because of his disease, he was invited for a genetic counselling with his healthy pregnant partner. In the patient, the diagnosis of SMDK was confirmed by molecular genetic analysis using classical sequencing of

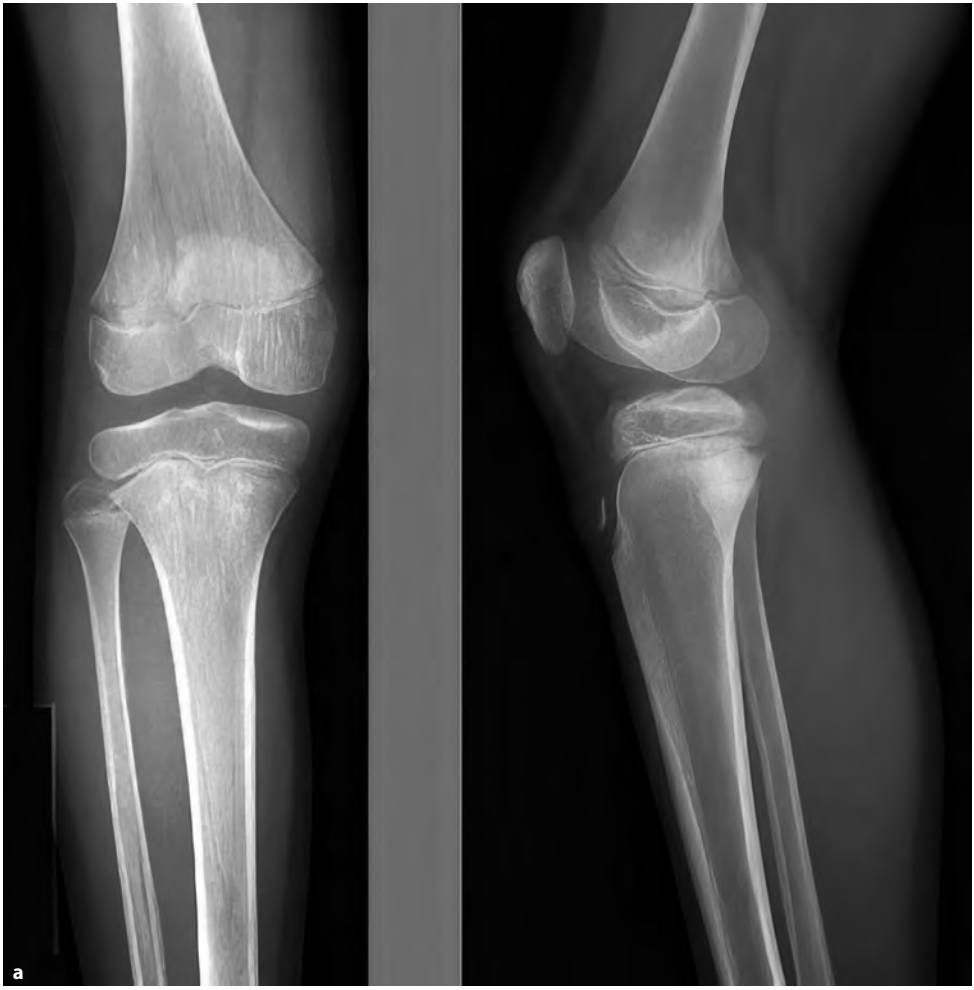
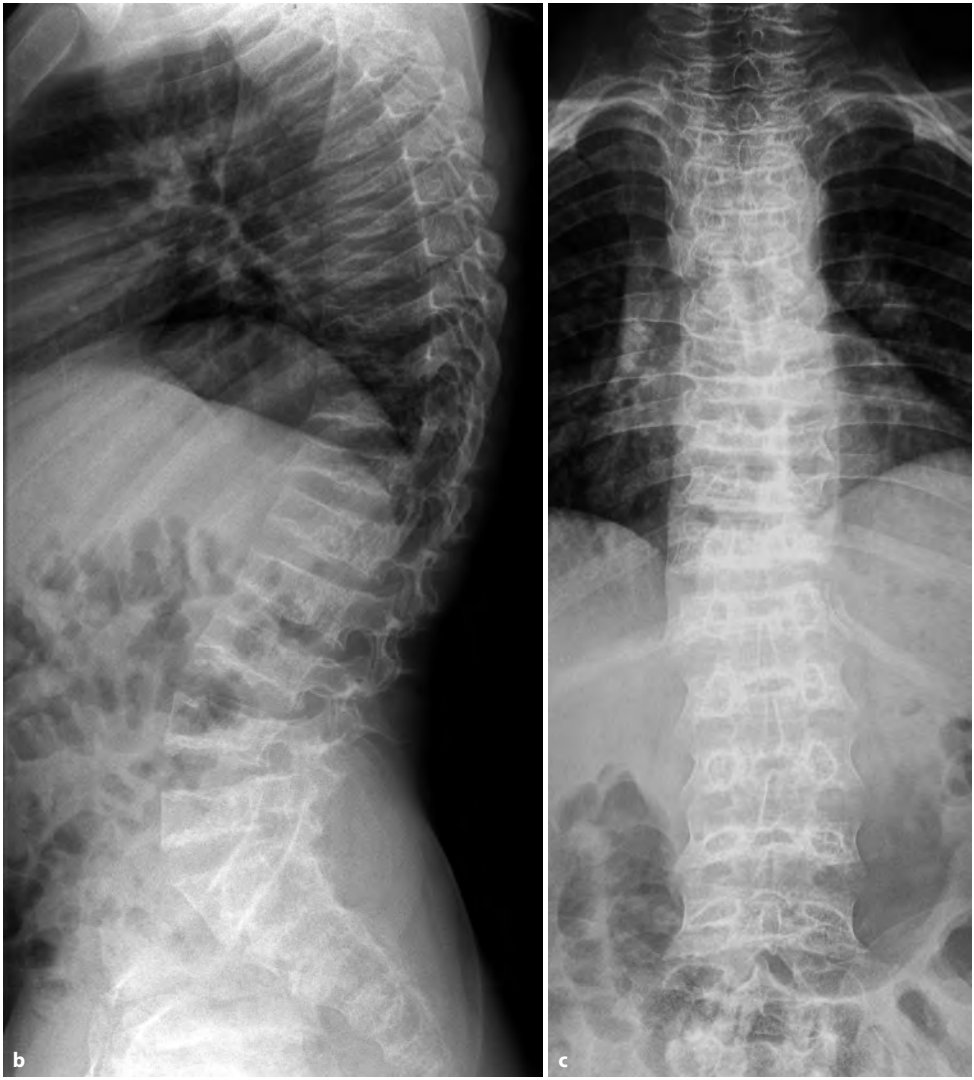


Figure 1 a–e: Radiographs of CASE I at 13 years of age: **a**: AP and lateral knee projection: Minimal metaphyseal irregularity, very narrow growth cartilage, abnormal ossification of tibial tuberosity – a typical finding in morbus Osgood – Schlatter. **b, c**: Long format spine AP and lateral projection: Thoracolumbar kyphosis and lumbar hyperlordosis. Platyspondyly with anterior wedging of the thoracic vertebrae. Note the additional bony buildup in the posterior two-thirds of the lower thoracic bodies and the upper lumbar spine. **d**: Pelvis and hips in AP projection: broad and short basilar portions of the iliac bones. Horizontal acetabular roofs. Short femoral necks with severely dysplastic proximal femoral metaphyses. Normal proximal femoral epiphyses. **e**: Left hand in AP projection: delayed bone age, narrow radial growth cartilage and minimal metaphyseal irregularity.



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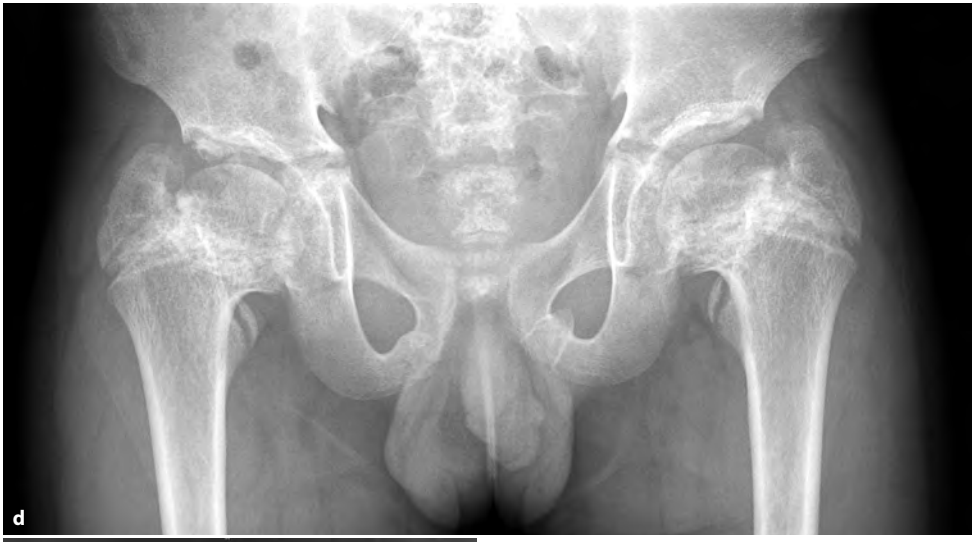


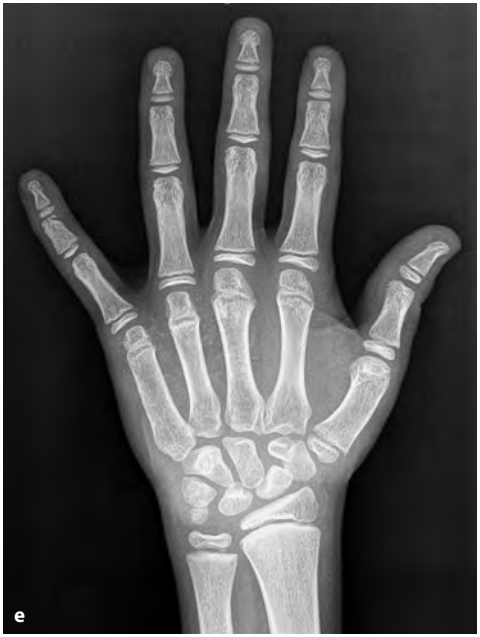


Figure 1 a–e: Radiographs of CASE I at 13 years of age: **d**: Pelvis and hips in AP projection: broad and short basilar portions of the iliac bones. Horizontal acetabular roofs. Short femoral necks with severely dysplastic proximal femoral metaphyses. Normal proximal femoral epiphyses. **e**: Left hand in AP projection: delayed bone age, narrow radial growth cartilage and minimal metaphyseal irregularity.

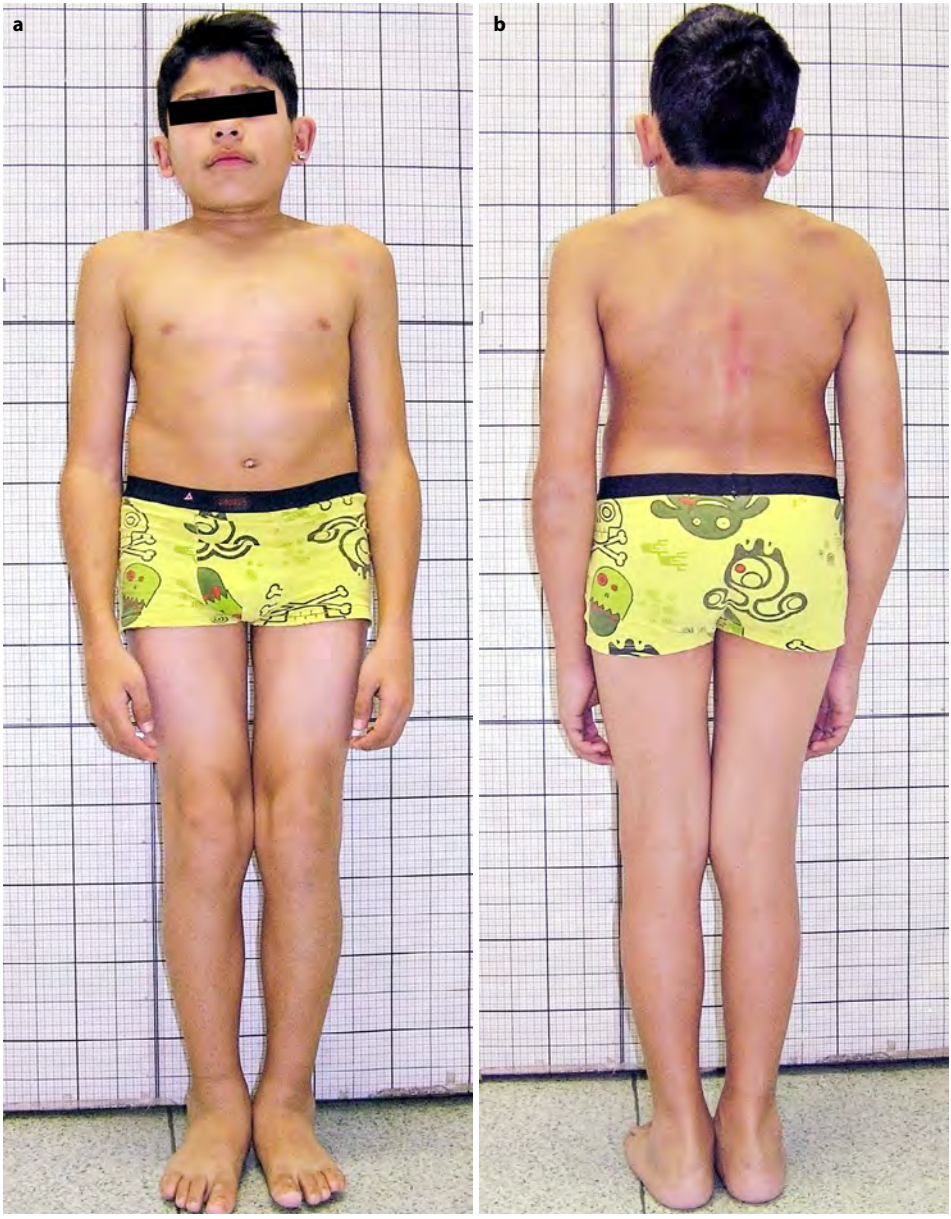


Figure 2 a–f. CASE I at 14 years and 3 months: height 131.7 cm (-4.9 SD), weight 37.7 kg (-2.3 SD), disproportionate stature with short neck and trunk – sitting height 64.5 cm (-4.8 SD), anterodorsal extension of the thorax – thoracic index 94.5 (3.9 SD), fixed kyphoscoliosis. **b**: note the erythema in the thoracic and lumbar spine caused by the corset

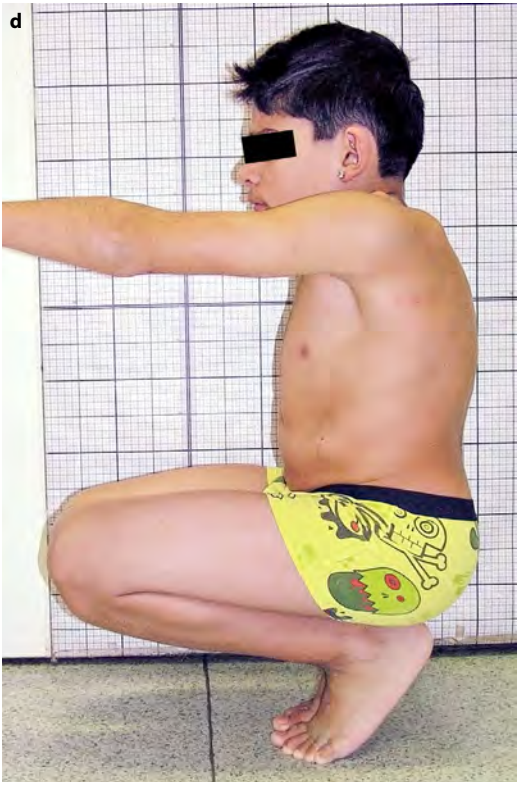


Figure 2 a–f. CASE I at 14 years and 3 months: **c:** shows mild limitation of extension at the knee joints and **d**: documents unrestricted flexion at the knee joints;

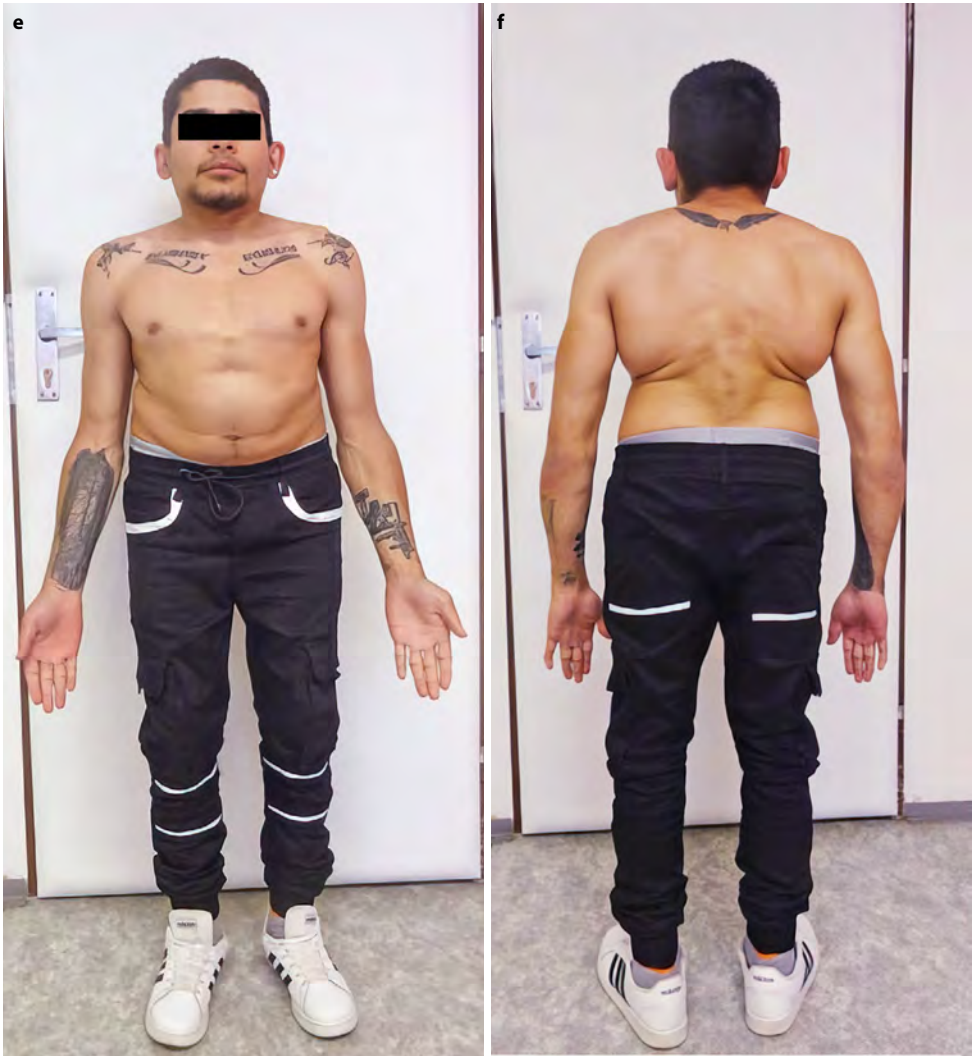


Figure 2 a–f. CASE I at 17.5 years: height 142 cm (-5.4 SD), weight 50.2 kg (-2.4 SD), BMI 24.9 (1.2 SD) siting height 68 cm, arm span 168 cm (118.3 % body height), head circumference 54.5 cm (-1.4 SD) cm, thoracic circumference 91.5 cm (-0,1 SD), thoracic index 100.8 (4.9 SD).

the *TRPV4* gene, which revealed a heterozygous mutation c.1781G>A (p.Arg594His) in exon 11 of the *TRPV4* gene (**2**). On the basis of a 50% risk of the transmission of the SMDK, the partners were offered prenatal diagnostics via amniocentesis, which they refused, and did not come for any further check-ups until the childbirth.

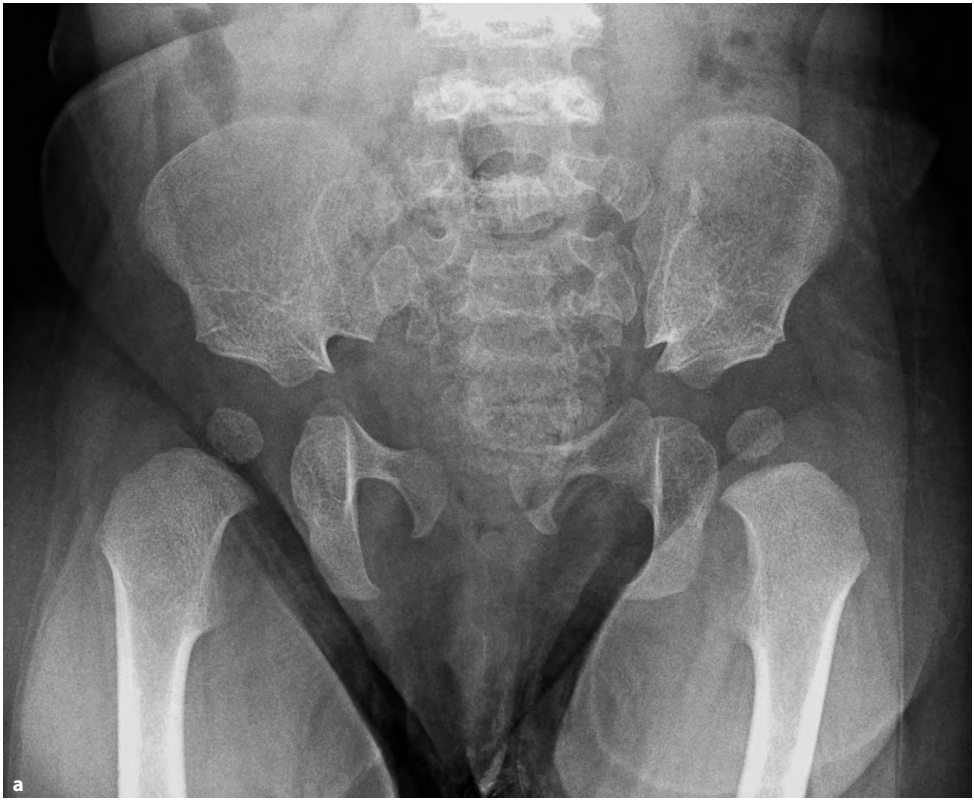
CASE II is a 22-month-old female, who was born from the first pregnancy of a 16-year-old healthy Caucasian mother (height 158 cm) and a 22-year-old father with SMDK (CASE I). Parental consanguinity was ruled out. Prenatally, during the 17th week of pregnancy, a standard ultrasound was carried out and no developmental disorders were found. The screening for Down syndrome was negative. The patient was born in term, the body weight was 3080 g (the 50th percentile of the Czech State Health Institute Growth Chart (GC)), and the length was 49 cm (the 30th percentile). There were no specific signs of SMDK after the delivery. At 10 months, the girl weighed at 8610 g (the 10th percentile), she was 69 cm long (the 30th percentile), the overall psychomotor development was physiological. The diagnosis was confirmed at the same age by molecular genetic analysis, which revealed a heterozygous mutation c.1781G>A (p.Arg594His) in exon 11 of the *TRPV4* gene (**2**). This mutation was previously identified as the cause of SMDK also in her father. At 14 months, she was 73.5 cm tall (-1.3 SD), weight 9.2 kg (-0.9 SD) (both the 10th percentile), BMI 17 (0 SD). The figure was proportional (crown-rump length 47 cm, ratio crown-rump length subischial leg length 63.9% /0.4 SD/). Apart from a slightly triangular mouth (downwardly oriented mouth corners) and hypertelorism, there was no other significant orofacial stigma. No pathologic limitations in the extension of the elbows or hip joints were found, and the spine was not scoliotic nor hyperkyphotic (see **Figure 4 a–c**). Radiographs showed typical radiologic signs of SMDK (see **Figure 3 a–c)**. This CASE confirms the autosomal dominant inheritance of SMDK.

The first patient (CASE I) has 4 brothers, 3 of them also present clinical symptoms of SMDK, however, no genetic tests were done in their cases. The last of the brothers has not undergone any clinical examination. The father of CASE I also has typical clinical symptoms of SMDK, he is 133 centimetres tall. See pedigree – **Figure 5**.

DIAGNOSIS and DIFFERENTIAL DIAGNOSIS

Before the molecular genetic cause of the disease was known, most cases were diagnosed after the age of two and more based on knowledge of clinical and radiological signs. Bieganski et al. **(2)** in a case with SMDK that was caused by substitution of c.1781G>A (p.Arg594His) in exon 11 of the *TRPV4* gene revealed abnormal ossification and notochordal remnants in discs and vertebrae. In young children, typical signs are not yet found clinically or radiologically, but MRI already shows deviations from the norm.

Molecular diagnostics allows a timely diagnosis before the onset of clinical symptoms; therefore the patient and his parents do not have to go through expensive and burdensome examination. Another benefit is the possibility of preimplant or prenatal diagnosis in families with the occurrence of SMDK. As a result, the generational transmission of the disease can be stopped (**9**). This option was also offered to our patient.



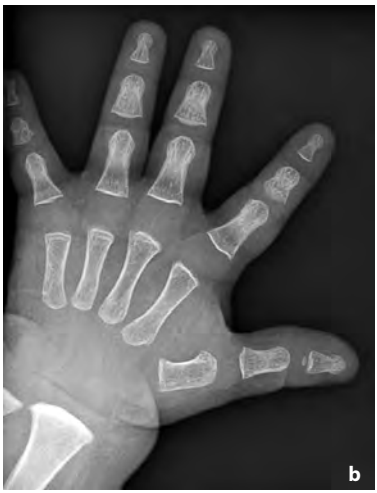


Figure 3 a–c: Radiographs of CASE II at 14 months: **a**: pelvis and hips in AP projection: The iliac bones are broad, the sacrosciatic notches are narrow, the basilar portions of the iliac bones are broad and short. The femoral necks are somewhat short, no major metaphyseal abnormalities are seen, the ossification centres of both femoral heads are round, well circumscribed, proximal femoral epiphyseal plates are wide. **b**:left hand in AP projection: delayed bone age, the tubular bones of the hand are short with metaphyseal irregularities

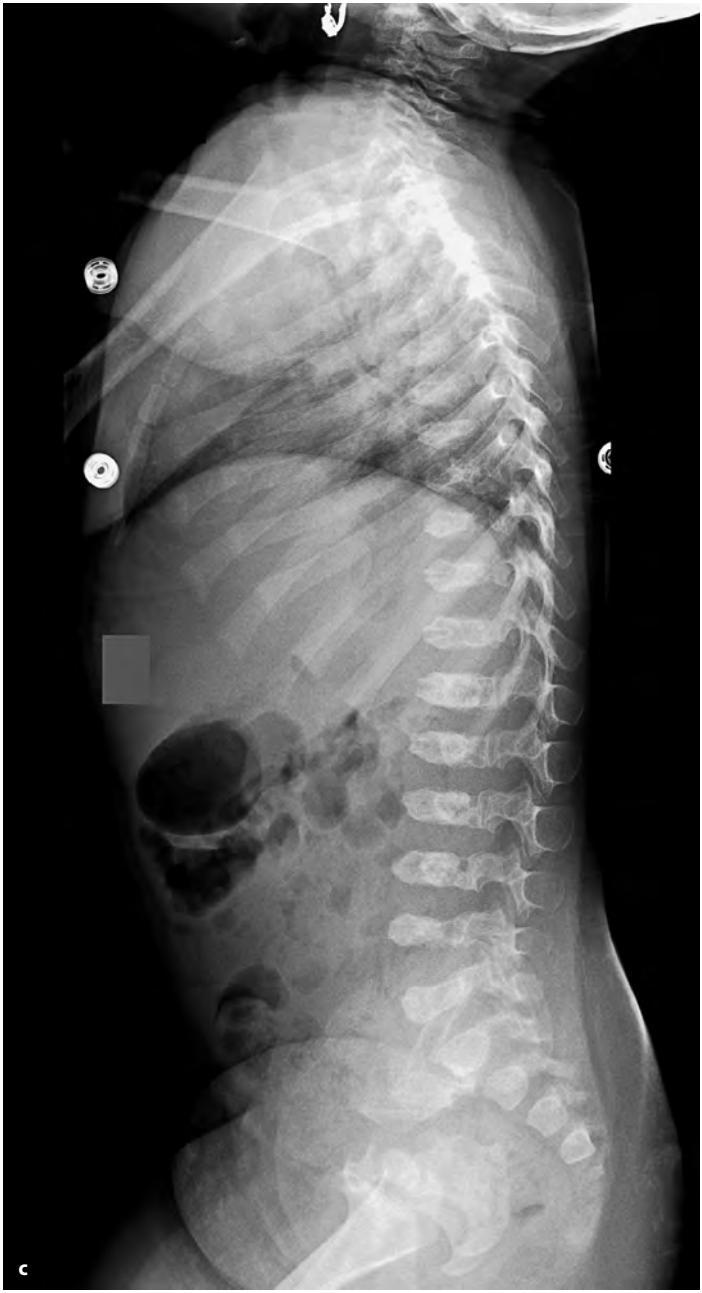


Figure 3 a–c: Radiographs of CASE II at 14 months: **c**: spine in lateral projection: the vertebral bodies are flat with some anterior wedging. Note anterodorsal enlargement of the thorax.

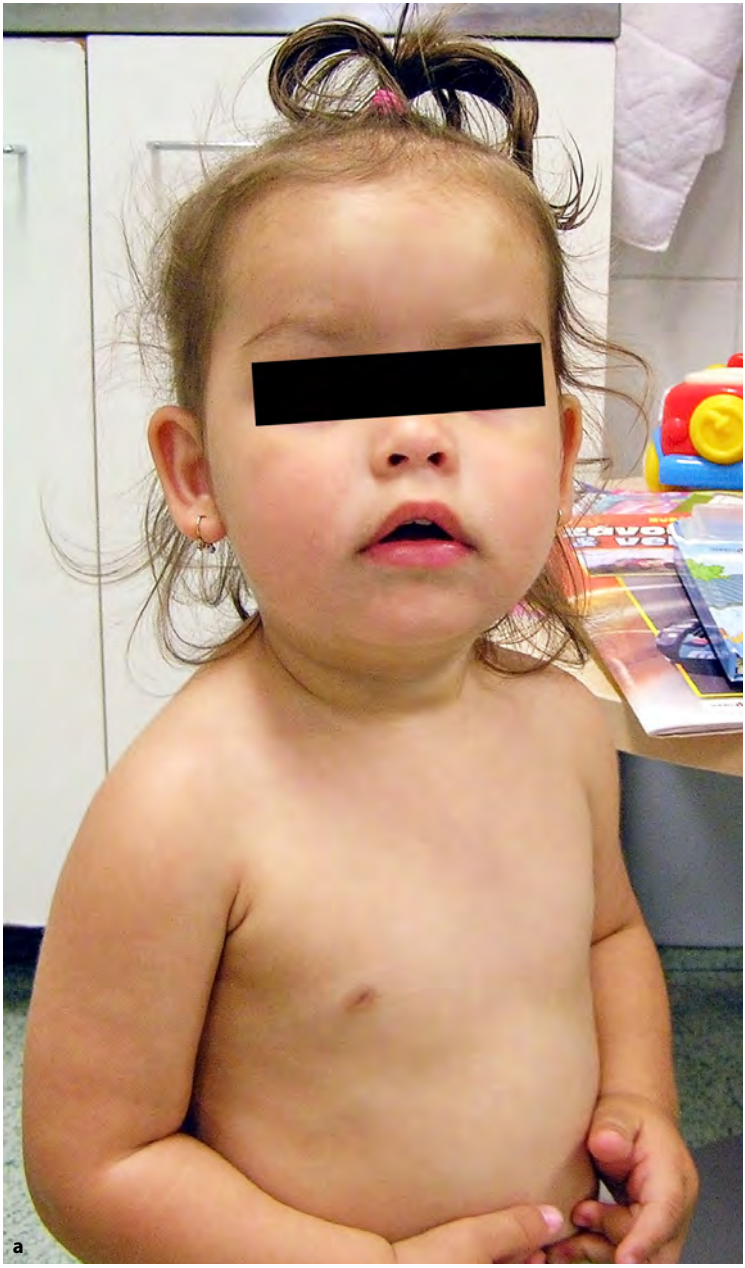
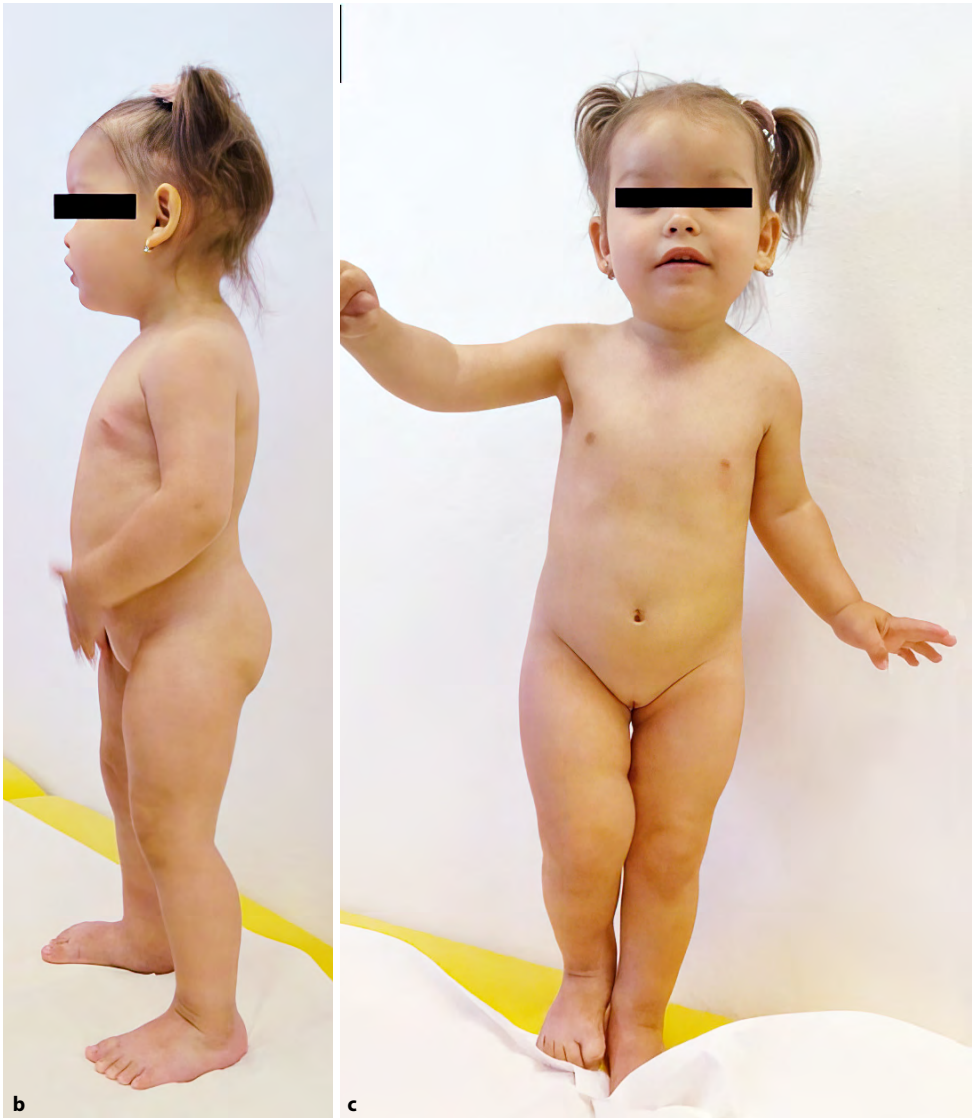


Figure 4 a–c: CASE II at 22 months, slightly triangular mouth, low-set ears, proportional figure



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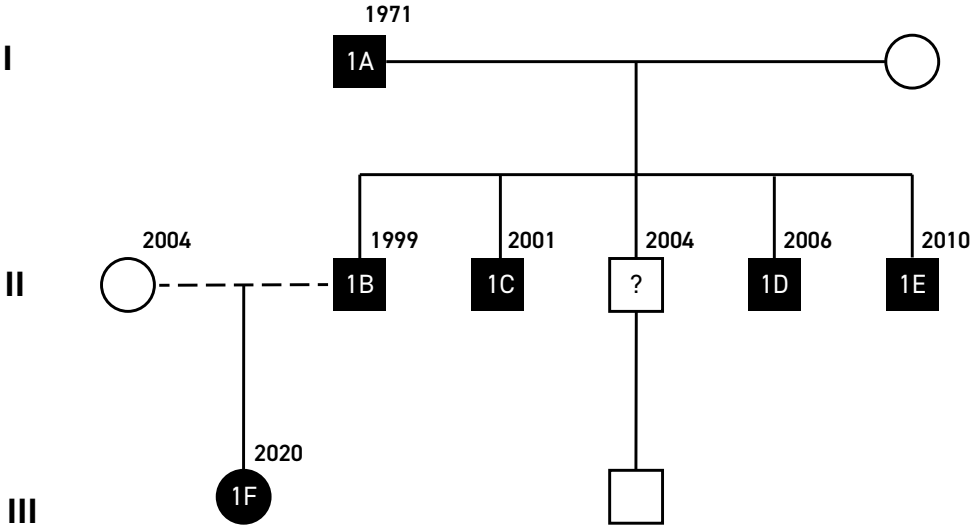

Figure 5: The pedigree of six affected members of the one family over three generations. 1B and 1F – the diagnosis was confirmed by molecular genetic testing; 1A, 1C, 1D, 1E – patients with clinical and radiological symptoms of SMDK.

Krakow et al. **(4)** identified heterozygosity for missense mutations in the *TRPV4* gene in 6 patients with SMDK. The mutations in *TRPV4* gene modify basal calcium channel activity and except SMDK, they are cause of several other autosomal dominant disorders. These include neuromuscular disorders, such as Charcot-Marie-Tooth neuropathy type 2C or congenital distal spinal muscular atrophy. Skeletal dysplasias with *TRPV4* mutation include, among other, autosomal dominant brachyolmia, metatropic dysplasia and spondyloepiphyseal dysplasia (Maroteaux type) (**9**).

The diagnosis of SMDK is established in a proband with suggestive clinical and radiological findings by molecular genetic testing. If there is a significant suspicion for this disease, classic sequencing can be used. If the phenotype is not typical and the differential diagnosis is wider, a multigene panel examination that includes *TRPV4* and other genes of interest is indicated. Depending on the performing laboratory, the panels contain various genes. For multigene panels, the next-generation sequencing (NGS) is used. NGS is a cost – effective method which allows simultaneous testing of hundreds of genes (**9, 14**).

The **differential diagnosis** includes **Metatropic dysplasia** which differs by the presence of dumbbell-shaped long tubular bones, more severe epiphyseal dysplasia, and crescent-shaped iliac wings. And **Pseudo-Morquio disease II** (spondyloepiphyseal dysplasia Maroteaux type) where the radiographs usually reveal varying degrees of platyspondyly but less metaphyseal and more epiphyseal involvement. These symptoms are not typically found in patients with SMDK (**12**). Other disease,

which should also be ruled out, is the autosomal dominant **Brachyolmia, type 3** that is also caused by the mutations in the *TRPV4* or *COL2A1* gene. All these diseases could also be diagnosed by using classical sequencing or NGS (**1, 3**).

CONCLUSION

The CASE I was diagnosed with SMDK on the basis of family history and the radioclinical signs of the disease at 5.5 years of age. Marik et al. published the patient and his family cases in 2006. At that time, molecular genetic testing was not available.

Considering the radioclinical diagnosis of SMDK, the CASE I was invited for a genetic counseling with his healthy pregnant partner. Through molecular genetic testing, we were able to confirm the diagnosis of SMDK in CASE I, and also in his daughter (CASE II). In CASE II, the diagnosis was confirmed at very young age, when no radiological and clinical findings have been submitted.

The only treatment available for SMDK is generally symptomatic and supportive. Long-term rehabilitation is the method of choice from preschool age. According to the authors' experience, the progression of ventrodorsal chest enlargement and thoracic kyphoscoliosis can be favourably influenced by consistently guided corset therapy during the growth period.

Acknowledgements

Our thanks and admiration go to Doc. Dr. Med. Kazimierz S. Kozlowski M.R.A.C.R. (Sydney, Australia) for his long-standing cooperation in the field of genetic skeletal disorders, especially in the clinical and radiological diagnosis.

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ŽIVOTNÍ JUBILEA
ANNIVERSARIES

RNDr. Jaroslav Jambor – devadesát let

RNDr. Jaroslav Jambor se narodil se 30.6. 1932 v Třešti u Jihlavy. Otec byl návrhářem nábytku. Firma v krizi zbankrotovala. Přestěhovali se nejdříve do Kolína a pak, když bylo Jaroslavovi šest let do Brna. Tam se narodili dva sourozenci.

V Brně Jaroslav ukončil základní školu, V roce 1946, když chodil do měšťanské školy, přivedl jej oblíbený učitel k elektronice a přírodovědným oborům. Na gymnáziu jej zaujala chemie. Během gymnaziálních studií si udělal státnici z těsnopisu. Na gymnáziu měl v 16 letech úraz, po kterém mu byla amputována levá ruka. Na reálném gymnáziu maturoval v roce 1951.

Na přírodovědné fakultě si vybral obor chemie a fyziky. Byl to dvouletý studijní základ, po kterém pokračovala specializace již v analytické chemii.

Na fakultě jej zaujal prof. Okáč, který řídil katedru chemie, znamenitý pedagog s vysokou autoritou. Na fakultě pod jeho vedením zkoumal barevné komplexy pro detekci či zkoncentrování analytu. V diplomové práci se soustředil na „Stanovení zinku pomocí redoxních činidel".

V roce 1956 ukončil studium na PřF UJEP, obor analytické chemie. Na základě umístěnky vzal Jaroslav místo metalurga ve Škodových závodech v Plzni. Stal se referentem pro výrobnu ocelí. V Plzni působil v letech 1956 až 1958. Do Brna se vrátil jako chemik Ústavu hydrodynamiky AV. Pracoval na čiřičích, zařízeních na čistění vody. Spolupracoval na vývoji pojízdné jednotky pro čistění vody zamořenou radioaktivním spadem. V uvedeném ústavu pracoval od roku 1958 do roku 1962.Vzhledem k tomu, že se ústav stěhoval do Prahy, přešel v roce 1963 do Ústavu vlastností kovů AV v Brně. Pracoval zde rok na analýze vměstků v ocelích a zkoumal též vysokoteplotní slitiny pro turbíny.

V roce 1964 Jaroslav nastoupil na Katedru analytické chemie PřF UJEP, kterou ještě vedl prof. Okáč. Zde zavedl spektrální analýzu. Tato metoda se používala pro kvantitativní, ale především pro kvalitativní účely, kde je výhodou vysoká citlivost metody, takže je možné dokazovat stopové obsahy prvků i ve složitých vzorcích, například při restaurování obrazů.

Na katedře Jaroslav vybudoval elektronickou dílnu spolu s prof. Otrubou, ve které byly konstruovány atypické elektronické přístroje. Jedním z nich byl i emisní plamenný fotometr s vysokým spektrálním rozlišením a nízkým rozptýleným zářením.

Zájem Jaroslava o elektroniku vyústil v získání vysílací koncese.

V roce 1974 spustil Jaroslav spolu s prof. Otrubou první ICP (Inductively coupled plasma) výboj v tehdejším Československu. Postupem času se dařilo spektrální laboratoř katedry vybavovat stále modernějšími přístroji.

ICP spektrometrie a další nové metody byla zavedeny do výuky analytické chemie i do výzkumných projektů.

V roce 1984 RNDr. Jambor s MUDr. Smrčkou zavedli v Československu nový obor na rozhraní archeologie a paleoantropologie – rekonstrukci stravy a prostředí pravěkých populací na základě analýzy stopových prvků z kosterních populací lidí a zvířat. V současné době se tento směr studia zařazuje pod termín bioarcheologie. Vytvořený tým stanovil přesně určená odběrová místa z lidského i zvířecího skeletu, provedli srovnání skeletů uložených v zemi i u kadaverů. Jaroslav stanovil přesná pravidla pro hodnocení diageneze, podle uložení kosterních pozůstatků v půdě. Získané poznatky se ukázaly nezastupitelné právě u pravěkých populací, kde nejsou žádné písemné památky.

V roce 1998 Jaroslav odešel do důchodu. Stále se však zajímá o restaurování památek a současný rozvoj analytické chemie.

Ještě roce 2021 ve svých 89 letech Jaroslav pomáhal s korekturami kapitol interpretujícími výsledky analýz kostí a zubů z maďarských a moravských lokalit pro knihu: *„Health and disease in Neolithic Lengyel Culture."* (2021).

Jménem výboru Společnosti pro pojivové tkáně České lékařské společnosti J.E. Purkyně panu kolegovi RNDr. Jamborovi děkujeme za jeho přínos pro rozvoj analytické chemie, originální metodiky určování stopových prvků ve skeletu a při příležitosti jeho jubilea mu ze srdce přejeme pevné zdraví a spokojenost v kruhu rodiny.

Za Společnost:

prof. MUDr. Václav Smrčka, CSc.
člen výboru

prof. MUDr. Ivo Mařík, CSc.
předseda

INFORMACE O SPOLEČNOSTI PRO POJIVOVÉ TKÁNĚ ČLS J. E. PURKYNĚ (SPT)

Vážená paní kolegyně, vážený pane kolego,

dovolujeme si Vás informovat o možnosti stát se členem **Společnosti pro pojivové tkáně** (SPT), která v roce 2004 navázala na plodnou desetiletou činnost Společnosti pro výzkum a využití pojivových tkání vedenou panem prof. MUDr. M. Adamem, DrSc. Posláním SPT je podpora rozvoje výzkumu pojivových tkání, šíření nových poznatků týkajících se všestranných analýz tkání z obecného pohledu, moderních klinických přístupů k diagnostice a léčbě. Dalším posláním SPT je usnadnění styků mezi jednotlivými odborníky navázáním spolupráce s různými vědeckými, odbornými, výrobními a farmaceutickými společnostmi.

Vědecké poznání a aplikace nejnovějších poznatků v klinické praxi nabyly v posledních letech nebývalého zrychlení, a to nejenom v zahraničí, ale i u nás. Tato skutečnost bezprostředně souvisí s kvalitativním rozvojem poznání i v nebiologických vědách a v moderních inženýrských přístupech. Stále více se prokazuje, že vše se vším souvisí – není náhodou, že nové poznatky a objevy vznikají na rozhraní oborů a různých vědních disciplín. Lidská společnost v posledních desetiletích dosáhla nové civilizační kvality – ve vědě a v jejich aplikacích zcela jistě, avšak v morálce a etice ne tak příliš. Biomedicína je v současné době rozsáhlou interdisciplinární vědou, která bez kooperace s jinými vědními obory by byla odsouzena ke stagnaci. Proto cílem SPT je nejenom integrovat odborníky v biomedicíně, ale i v technických sférách.

Prioritní snahou SPT je presentovat odborné veřejnosti a specialistům v klinické praxi nejnovější poznatky v oblasti pojivových tkání. SPT je i společenskou organizací klinických pracovníků, vědců, pedagogů, která si klade za cíl společensky sblížit nejenom pracovníky v aktivní službě, ale i kolegyně a kolegy v důchodovém věku a v neposlední řadě i studenty a mladé doktorandy z vysokých škol, universit a akademických ústavů.

SPT organizuje během každého roku alespoň dvě odborná a společenská setkání, kde vedle odborných přínosů je kladen důraz také na společenské – přátelské diskuse všech vás, kteří nechtějí stagnovat a kteří nechtějí přemýšlet o nových poznatcích izolovaně a osamoceně.

Pro uhrazení nejzákladnějších nákladů na korespondenci se členy společnosti, jejich informovanost a pořádání odborných kolokvií, symposií a společenských odborných setkání byl stanoven **roční členský příspěvek pro aktivní kolegyně a kolegy 200 Kč** a **pro studenty a důchodce 100 Kč.**
SPT vydává časopis Pohybové ústrojí – pokroky ve výzkumu, diagnostice a terapii, do kterého se i vy můžete aktivně zapojit odbornými články a vašimi zkušenostmi. **Pro současné odběratele časopisu PU a další zájemce doporučujeme přihlásit se na http://www.pojivo.cz/en/newsletter/, zadat jméno a e-mailovou adresu, na kterou bude časopis posílán. Na webové doméně SPT ČLS JEP http://www.pojivo.cz/cz/pohybove-ustroji/ naleznete ve formátu PDF všechna jednotlivá čísla a dvojčísla časopisu (včetně Suplement) vydaná od roku 1997 (bezplatný přístup).**
Milí kolegové, nestůjte opodál a připojte se k české inteligenci – v oblasti pojivových tkání, ke které i Vy zcela jistě patříte. V naší krásné české zemi je třeba, aby prameny poznání byly stále živé a permanentně udržované. Poslání každého z nás není náhodné. Jsme velice zavázáni našim předkům, kteří rozvíjeli kvalitu odbornosti v naší zemi. Nepřipusťme útlum vědy u nás. Nenechme se zmanipulovat programovanou lhostejností, vyrůstající z neodbornosti, závisti a z patologického prosazování ekonomicko-mocenských zájmů.

Těšíme se na Vás a na Vaše zkušenosti – přijďte mezi nás!

Za výbor společnosti:

Prof. MUDr. Ivo Mařík, CSc. – předseda
Prof. MUDr. Josef Hyánek, DrSc. – čestný předseda
Prof. Ing. Miroslav Petrtýl, DrSc. – místopředseda
RNDr. Martin Braun, PhD – vědecký sekretář
Ing. Jana Zelenková – pokladník

Přihlášku do Společnosti pro pojivové tkáně ČLS JEP, z.s. najdete na adrese:
http://www.pojivo.cz/cz/wp-content/uploads/2020/02/PrihlaskaCLS_JEP_SPT_form.pdf

Přihlášku do Ortopedicko-protetické společnosti ČLS JEP, z.s. najdete na adrese:
http://www.pojivo.cz/cz/wp-content/uploads/2020/02/PrihlaskaCLS_JEP_OPS_form.pdf

INFORMATION ABOUT SOCIETY FOR CONNECTIVE TISSUES CMA J. E. PURKYNĚ (SCT)

Dear Sir/Madam, dear Colleagues,

We have great pleasure to inform you about the possibility of joining the **Society for Connective Tissues** (SCT) that was established in 2004 in order to continue the ten-year fruitful activities of the Society for Research and Use of Connective Tissue headed by Professor M. Adam, MD, DSc. The activities of the SCT are aimed at supporting the research development in the field of connective tissues, the dissemination of knowledge related to the all-purpose analyses of the tissues in general, and the application of the up-to-date approaches to the diagnostics and clinical practice. Further, the SCT is determined to facilitate contacts between the respective specialists by means of collaboration with various research, professional, production and pharmaceutical companies.

In the last few years, the scientific knowledge and the application of the latest findings in the clinical practice have accelerated on an unprecedented scale, not only abroad, but also in this country. This fact is closely connected with the qualitative development of the knowledge in the non-biological sciences and in the up-to-date engineering approaches. The fact that all things are mutually connected is becoming more and more evident. It is fairly obvious that the new knowledge and discoveries arise on the dividing line between the different fields and disciplines of science. In the last few decades, the human society has reached the new qualities of civilization. This applies, in particular, for the disciplines of science and their applications; however, this statement can hardly be used with reference to the moral and ethical aspects of the human lives. At present, the biomedical science is a wide-ranging interdisciplinary science which, in case of lack of cooperation with other scientific disciplines, would be condemned to stagnation. That is the reason why the SCT is aimed at integrating the specialists both within the biomedical science and within the engineering fields.

The priority objective of the SCT is to present the professional public and specialists involved in the clinical practice with the latest knowledge in the field of connective tissues. The SCT is also a civic society whose aim is to bring people close together by joining members of the clinical staff, researchers and teachers including the retired ex-colleagues and, last but not least, the undergraduates and PhD students from universities and academic establishments.

The SCT is planning to organize at least two professional and social meetings each year. Beside the professional contribution of these meetings, emphasis will be laid on social activities – informal

discussions of all those who do not want to stagnate and who do not want to acquire the new knowledge in solitary confinement.

The annual membership fee is 200 Czech crowns for full workers, and 100 Czech crowns for students and pensioners. This membership fee shall be used to cover the basic costs on correspondence with the members of the Society in order to inform them about organizing colloquiums, symposiums and social meetings.

The SCT is also engaged in publishing of the interdisciplinary journal entitled **Locomotor System – Advances in Research, Diagnostics and Therapy**. You are invited to contribute to the journal writing professional articles, exchanging experience or, simply sharing your opinions. You can find the volumes of Locomotor System journal at http://www.pojivo.cz/cz/pohybove-ustroji/ since 1997 (free of charge). Since 2013 only electronic edition of the journal is available. That is why we recommend to all subscribers and those interested apply at http://www.pojivo.cz/en/newsletter, enter personal data, titles and e-mail address where the journal will be mailed.

Dear Colleagues, do not stand aside (suffering from terrible lack of time) and join the professional people in the field of connective tissues to whom you undoubtedly belong. In this beautiful country, the sources of knowledge should be kept alive and maintained permanently. Our role in this process is not accidental. We are much obliged to our ancestors who had developed the qualities of proficiency in this country. Do not allow the decline of science. Do not let the programmed indifference arising from lack of professionalism, enviousness, and pathological promotion of economic and power interests manipulate us.

We are looking forward to meeting you. We will be pleased if you join us and share your experience with us.

On behalf of the committee of the Society for connective tissues:

Professor Ivo Marik, MD, PhD – chairman
Professor Josef Hyánek, MD, DSc – honorary chairman
Professor Miroslav Petrtýl, MSc, DSc – vice-chairman
Braun Martin, Dr, PhD – research secretary
Zelenková Jana, Eng – treasurer

Membership application form of the Society for Connective Tissues, Czech Medical Association J.E. Purkynje, Prague you can find on the following link:
http://www.pojivo.cz/cz/wp-content/uploads/2020/02/PrihlaskaCLS_JEP_SPT_form.pdf

Membership application form of the Orthopaedic-Prosthetic Society, Czech Medical Association J.E. Purkynje, Prague you can find on the following link:
http://www.pojivo.cz/cz/wp-content/uploads/2020/02/PrihlaskaCLS_JEP_OPS_form.pdf

VZPOMÍNKA NA DR. JACQUESE CHÊNEAU
REMEMBERING DR. JACQUES CHENEAU (19.5.1927–14.7.2022)

Dr. Jacques Cheneau významně přispěl k nechirurgické léčbě skoliózy. Je třeba ho považovat za jednoho z největších mistrů v oblasti léčby korzetem. Koncept «Cheneau korzetu» se začal používat ve Francii pod názvem CTM = Cheneau-Toulouse-Münster (1979). V 90. letech 20. století vedl Dr. Cheneau řadu kurzů pro ortopedické techniky, aby je seznámil s myšlenkou svého korzetu, a tak se korzet Cheneau rozšířil v Německu, Francii, Rakousku, Švýcarsku, Itálii, Španělsku a dalších zemích, jako je Česká republika, Slovensko, Polsko a Ukrajina, Rusko, Bělorusko a další východoevropské země. Koncepce korzetu Cheneau se rozšířila i v dalších zemích, stal se populární i na jiných kontinentech, například v Americe, Asii a Africe, a postupně ovlivňoval mnoho dalších koncepcí korzetů po celém světě.

Dr. Jacques Cheneau has made significant contributions to the non-surgical treatment of scoliosis. He should be considered one of the greatest masters in the field of corset treatment. The concept of the "Cheneau corset" came into use in France under the name called CTM = Cheneau-Toulouse-Münster (1979). In the 1990s, Dr. Cheneau conducted a number of courses for orthopaedic technicians to introduce them to the idea of his corset, and so the Cheneau corset spread in Germany, France, Austria, Switzerland, Italy, Spain and other countries such as the Czech Republic, Slovakia, Poland, Ukraine, Russia, Belarus and other Eastern European countries. The concept of the Cheneau corset has also become popular in other continents such as America, Asia and Africa and gradually influenced many other corset concepts around the world.

Jacques Chêneau se narodil v Tunisu 14. května 1927. Medicínu studoval v Lyonu a později v Toulouse v letech 1946–51. V roce 1953 se přihlásil do vojenské akademie v Paříži a po krátkém výcviku se stal lékařem francouzských parašutistů ve Vietnamu. V roce 1954 byl vážně zraněn a od ledna do září vězněn ve Vietnamu. Po návratu z války v roce 1955 pracoval jako lékař v Toulouse, kde v roce 1962 získal certifikát pro rentgenologii. V roce 1964 získal certifikát ze sportovní medicíny. V roce 1968 působil jako asistent v nemocnici v Gaillac a Toulouse. V roce 1974 se stal specialistou v rehabilitaci. V letech 1985–1987 pracoval jako asistent v Centru pro těžké deformity páteře v Bad Wildungenu v Německu, které vedl Professor Dr. Zielke. Od roku 1987 do roku 2013 působil jako spojovací článek mezi universitami, klinikami a ortopedicko-protetickými pracovišti na celém světě.

S Dr. Chêneau jsme spolupracovali od roku 1998, kdy byl poprvé na pracovní návštěvě v Praze. Své životní zkušenosti publikoval v několika příspěvcích v časopisu Pohybové ústrojí a záhy se stal členem redakční rady časopisu. Při všech svých návštěvách v Praze osobně asistoval při tvarování pozitivních modelů českých dětí s deformitami páteře na ortoticko-protetickém pracovišti Ortotika s.r.o. zprvu v Truhlářské ulici v Praze 1, později po přestěhování v Praze Motole. V roce 2001 se aktivně zúčastnil Symposia "Locomotor System Disorders – biomechanical aspects of the treatment in childhood", které se konalo v Lékařském domě v Praze. O dva roky později se opět aktivně zúčastnil Mezinárodního antropologického kongresu "Anthropology and Society", který se konal v Praze a Humpolci v roce 2003. Ve stejném roce byl účastníkem The 4th Prague-Sydney Symposia "Diagnostics and Conservative Treatment of Congenital and Acquired Locomotor Apparatus Defects". V roce 2006 jsme pana profesora uvítali na The 7th Prague-Sydney-Lublin Symposiu v Praze, kde mu bylo uděleno *Honorary Membership of The Society for Connective Tissues, Czech Medical Association, J.E. Purkyne.*

Další naše setkání bylo v Lublinu při příležitosti Lublin-Praha-Sydney-Toulouse symposia v dubnu 2007, které velmi zdařile zorganizoval pan professor Tomasz Karski, M.D., PhD. O měsíc později jsme se sešli s Jacquesem Chêneau v Regensburgu při oslavě jeho 80. narozenin. Při této příležitosti byl Dr. Cheneau oceněn medailí *Appreciation of Merits for Scientific progress of The Society for Connective Tissues, Czech Medical Association, J.E. Purkyne.*

1. návštěva Dr. Jacquese Cheneaua v Praze (24.–26. ledna 1998). Dr. Jacques Cheneau a ing. Pavel Černý vytvářejí sádrový pozitiv korzetu.
1st visit of Dr. Jacques Cheneau to Prague (24–26 January 1998). Dr. Jacques Cheneau and Ing. Pavel Černý creating a plaster positive of a corset.

Mezinárodní vědecké sympozium na počest 80. narozenin prof. Dr. Jacquese Chêneaua, 11.–13. května 2007, Regensburg. Jacques a jeho dcera Francois.
The International Scientific Symposium to Honour for the 80th Birthday of Prof. Dr. Jacques Chêneau, May 11–13, 2007, Regensburg. Jacques and his daughter Francois.

Dr. Jacques Cheneau was a member of the international editorial board of the journal Locomotor System – Advances in Research, Diagnosis and Therapy for 20 years – since 2002.

Jacques Chêneau was born in Tunis on 14 May 1927. He studied medicine in Lyon and later in Toulouse from 1946–51. In 1953 he enrolled in the military academy in Paris and after a short training became a doctor for French paratroopers in Vietnam. In 1954 he was seriously wounded and imprisoned in Vietnam from January to September. After returning from the war in 1955, he worked as a physician in Toulouse, where he became certified in radiology in 1962. In 1964, he became certified in sports medicine. In 1968, he worked as an assistant at the hospital in Gaillac and Toulouse. In 1974, he became a specialist in rehabilitation. From 1985 to 1987 he worked as an assistant at the Center for Severe Spinal Deformities in Bad Wildungen, Germany, headed by Professor Dr. Zielke. From 1987 to 2013, he served as a liaison between universities, clinics and orthopaedic-prosthetic departments worldwide.

We have worked with Dr. Chêneau since 1998, when he first visited Prague on a working visit. He published his life experiences in several articles in the journal Movement System and soon became a member of the editorial board of the journal. During all his visits to Prague he personally assisted in shaping positive models of Czech children with spinal deformities at the orthotic-prosthetic workplace Ortotika s.r.o., first in Truhlářská Street in Prague 1, later after moving to Prague Motol. In 2001 he actively participated in the Symposium "Locomotor System Disorders – biomechanical aspects of the treatment in childhood", which was held in the Medical House in Prague. Two years later, he again actively participated in the International Anthropological Congress "Anthropology and Society" held in Prague and Humpolec in 2003. In the same year he was a participant of The 4th Prague-Sydney Symposium "Diagnostics and Conservative Treatment of Congenital and Acquired Locomotor Apparatus Defects". In 2006, we welcomed him to The 7th Prague-Sydney-Lublin Symposium in Prague, where he was awarded *Honorary Membership of The Society for Connective Tissues, Czech Medical Association, J.E. Purkyne*.

Our next meeting was in Lublin on the occasion of the Lublin-Prague-Sydney-Toulouse Symposium in April 2007, which was very successfully organized by Professor Tomasz Karski, M.D., PhD. A month later we met Jacques Chêneau in Regensburg to celebrate his 80th birthday. On this occasion, Dr. Cheneau was awarded *the Appreciation of Merits for Scientific Progress Medal of The Society for Connective Tissues, Czech Medical Association, J.E. Purkyne*.

The following are important papers published by Dr. Cheneau in the journal Locomotor System – advances in research, diagnosis and therapy:

- CHÊNEAU J. Bracing scoliosis, 1997. *Locomotor System* 5, 1998, No. 1–2: 60–73.
- CHÊNEAU J. Scoliosis correcting brace. *Locomotor System* 9, 2002, No. 1–2: 33–40
- CHÊNEAU J. The brace, from 1970 to our times. Some results. *Locomotor System* 9, 2002, No. 3–4, p. 5–16.
- CHÊNEAU J. Wedged vertebrae expanded towards symmetry by brace. Two clinical cases. *Locomotor System* 13, 2006, No. 3–4: 165–177.

- CHÊNEAU J., KOTWICKI T., GRABSKI H., CHEKRYSHEV D. The way of adjusting brace which can be considered as a half module. *Locomotor System* 15, 2008, No. 1–2: 26–38.
- CHENEAU J., CHEKRYSHEV D., MEZENTZEV A. PETRENKO D. Treatment of the congenital scoliosis by Cheneau's brace. The first experiences. *Locomotor System* 16, 2009, No. 1–2: 23–30.
- CHÊNEAU J., HADDAM M., HADDAM Z., SLUP J. The brace 2013: 9 elective mechanisms of action. Three levels to be treated. *Locomotor System* 20, 2013, Suppl. No. 3–4: 285–286.

Dear Jacques, thank you!

Yours pupils in the Czechia

Poslední setkání s Jacquesem Cheneauem v jeho letním sídle ve vesnici Augeac u Le Puy ve Francii. Vlevo MUDr. Petr Krawczyk, uprostřed doktor Jacques Cheneau, vpravo profesor Ivo Mařík, CSc., srpen 9, 2017.
Last meeting with Jacques Cheneau at his summer residence in village Augeac near Le Puy in France. On the left Petr Krawczyk, MD, in the middle Assist. Professor Jacques Cheneau MD, on the right Professor Ivo Mařík, MD, PhD, August 9, 2017.

TÉMATIKA PŘÍSPĚVKŮ

K uveřejnění v časopise Pohybové ústrojí se přijímají rukopisy prací z oblasti pohybového ústrojí člověka, které se týkají především funkce, fyziologického i patologického stavu kosterního a svalového systému na všech úrovních poznání, diagnostických metod, ortopedických a traumatologických problémů, příslušné rehabilitace a léčebné i preventivní péče. Předmětem zájmu jsou týmové práce z oboru dětské ortopedie a osteologie, dále problémy z oboru biomechaniky, patobiomechaniky a bioreologie, biochemie a genetiky. Redakce časopisu má zájem publikovat články kvalitní, vysoké odborné úrovně, které přinášejí nové poznatky, jsou zajímavé z hlediska aplikací a nebyly doposud nikde uveřejněny s výjimkou publikace ve zkrácené formě.

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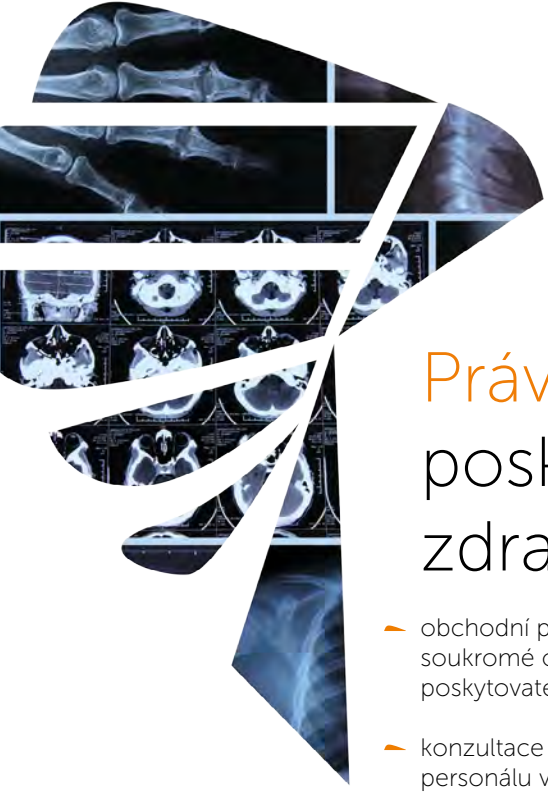

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