80 低リン血症性(ビタミンD抵抗性)くる病
Hypophosphatemic rickets

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定義・概念：くる病は骨・軟骨の石灰化障害によって引き起こされる疾患で，成長軟骨帯の閉鎖以前に発症した場合に用いられる。成長軟骨帯の閉鎖後の成人においては骨軟化症とよばれる。低リン血症性(ビタミンD抵抗性)くる病は，ビタミンD欠乏性くる病についで多く，その大部分は遺伝性である。そのなかでもっとも頻度が高いのがX連鎖性低リン血症性くる病(X-linked hypophosphatemic rickets：XLH；MIM #307800)で，伴性優性遺伝形式をとるが孤発例も散見され，現在200以上の変異が報告されている。男女ともに発症するが，男児のほうが重度といわれている。頻度は2万人に1人といわれている。くる病，低リン血症の他に成長障害，腎臓からのリンの漏出，血清リン値に対して不適切な血中1,25水酸化ビタミンD〔1,25$(OH)_2$D〕値の低値を特徴とする。XLH以外の遺伝性低リン血症性くる病の原因遺伝子も同定されてきており後述する。通常，尿中リン排泄の亢進以外の症状を呈するFanconi症候群や腎尿細管性アシドーシスは含まれない。ここでは主にXLHについて述べる。

病態生理：骨は骨基質蛋白にカルシウム(Ca)とリンが沈着して形成される。成長軟骨帯においては，規則的に配列・分化した軟骨細胞が石灰化し，それが骨に置換される。低リン血症によって成長軟骨帯におけるリンが不足すると，この過程が障害され，不規則で石灰化していない軟骨が形成され，X線では骨端線の不整として現れる。遺伝性低リン血症性くる病でもっとも頻度が高いXLHの原因遺伝子として*PHEX*がXp22.1から同定され，血中線維芽細胞増殖因子23(FGF23)が増加していることが示されている。FGF23は主に骨組織の骨細胞，骨芽細胞において発現し，ホルモンとして，腎臓の尿細管に作用し，近位尿細管におけるⅡa型，Ⅱc型ナトリウム-リン共輸送担体の発現を抑制することで，リンの再吸収を減少させる。さらに，FGF23はビタミンDの活性化酵素である1α位水酸化酵素の発現を抑制し，不活性化酵素である24位水酸化酵素の発現を誘導することで，血中1,25$(OH)_2$D値を低下させ，腸管でのリンの吸収を抑制する。つまり，FGF23は腎臓でのリンの再吸収の低下と腸管でのリンの吸収の抑制を引き起こすことで血清リンを低下させる。*PHEX*の遺伝子産物はエンドペプチダーゼと推察されているが，現在のところ，FGF23との関係は不明である。また，FGF23のシグナル伝達には共受容体としてKlothoが必要であるが，Klothoはビタミンの活性化とリンの再吸収の場である近位ではなく遠位尿細管において発現しているため，尿細管におけるFGF23の詳細な作用伝達経路は明らかではない。

臨床症状：症状の重症度はさまざまである。一般的には歩行開始後に，成長障害，下肢の変形(O脚，X脚，内反股)，歩行の遅れ，歩行の異常で気づかれることが多い。骨の所見は骨にかかる重力や骨の成長速度に依存するため，長管骨の成長板に現れやすく，症状も歩行開始時期である1歳代に顕著となりやすい。症状としては成長軟骨帯周囲の腫脹が多く，膝関節や足関節，手関節によくみられる。前額部の突出や歯の異常が認められることがあり，歯の異常としてエナメル形成障害，歯髄腔拡大，齲歯や歯槽膿瘍がみられる。成人期の骨軟化症では骨痛，関節痛，偽骨折，腱や靱帯，関節膜の異所性石灰化，関節炎，骨棘が生じることがある。重度の場合，脊椎管狭窄症や仙腸関節の癒合がみられる。筋力低下，テタニーは認めない。

検査所見：X線所見として長管骨骨幹端のフレイング(毛羽立ち)，カッピング(盃状陥凹)，フレアリング(拡大)が認められる。膝関節に変化がとくに現れやすく，足関節や手関節でもみられる。骨量減少の所見がみられることもある。

血液・尿検査所見：血清リン値の低下を認め，血清1,25$(OH)_2$D値は正常ないし比較的低値で低リン血症に比べると不適当に低い。尿中リン排泄の指標である尿細管リン再吸収率(% TRP)(基準値：成人80～96%)や尿細管リン再吸収閾値(TmP/GFR)(基準値：成人2.3～4.3 mg/dL)は低値もしくは基準値下限を示す。血清Ca値や25水酸化ビタミンD値，副甲状腺ホルモン(PTH)値は正常である。血清アルカリホスファターゼ(ALP)値は高値である。血清FGF23値は高値であり(30 pg/mL以上)，低値を示すビタミンD欠乏性くる病との鑑別に有用である。異常所見としては血清ALP値の高値がまずみられ，乳児期後期に低リン血症がみられる。高Ca

尿症は認めない。ビタミンD欠乏を合併した場合，PTHや1,25(OH)$_2$Dが高値となることがある。血清リン値は新生児期に高く，その後低下するため注意が必要である。低リン血症は，乳児期では4.5 mg/dL以下，幼児期では4.0 mg/dL以下，年長児では3.5 mg/dL以下，成人では3.0〜2.5 mg/dL以下を目安とする。

診断基準・鑑別診断：くる病の症状およびX線所見および上記の検査所見から診断される。くる病はビタミンD作用不全，リン欠乏，その他の原因(低ホスファターゼ症，骨幹端骨異形成症，アルミニウムなどの薬剤，など)に大別される。前者の場合，ビタミンDの利用障害(日光照射不足，栄養摂取不足，腸管での脂質吸収障害，尿への漏出)，代謝障害(肝疾患，腎疾患，ビタミンD依存性くる病I型，フェニトイン，フェノバルビタール，リファンピシンなどの薬剤)，標的臓器の不応(ビタミンD依存性くる病II型)に分類できる。リン欠乏の場合，摂取不足(栄養摂取不足，腸管での吸収障害，水酸化アルミニウム)と尿への漏出〔XLH，autosomal dominant hypophosphatemic rickets (ADHR)，autosomal recessive hypophosphatemic rickets (ARHR)，Hereditary hypophosphatemic rickets with hypercalciuria (HHRH)，腫瘍随伴性くる病・骨軟化症(TIO)，Fanconi症候群，Dent病，線維性骨異形成症，腎尿細管性アシドーシス，バルプロ酸などの薬剤，など〕に分けられる。

ADHRは*FGF23*遺伝子の機能獲得型変異によるまれな疾患で，XLHと類似の臨床症状や検査所見を呈する。不完全な浸透度で遅発性の症例もみられる。ARHRは*DMP1*遺伝子の機能喪失型変異によるまれな疾患でXLHと類似の臨床症状や検査所見を呈する。*DMP1*は骨細胞や歯の象牙芽細胞において発現していて，ARHRにおいては血清FGF23値の増加がみられる。最近*ENPP1*遺伝子がARHRの原因遺伝子の一つとして同定された。HHRHはIIc型ナトリウム-リン共輸送担体をコードする*SLC34A3*遺伝子異常によるまれな常染色体劣性遺伝性疾患で，尿中リン排泄の増加，低リン血症，血清1,25(OH)$_2$D値の増加，血清PTH値の低下が認められる。二次性の高カルシウム尿症や腎結石，筋力低下を伴う。リンの補充のみで検査所見や骨病変は改善する。TIOは腫瘍による過剰がFGF23の産生によって生じる小児ではきわめてまれな疾患である。骨痛，筋力低下を呈する。線維性骨異形成症は*GNAS1*遺伝子の体細胞機能獲得型変異によるMcCune-Albright症候群の症状の一つで，骨病変とFGF23の増加を伴う低リン血症を認める。

治療方針：活性型ビタミンDと中性リン製剤で治療を行う。活性型ビタミンDはアルファカルシドール(1αOHD) 0.05〜0.1 μg/kg/日(1〜3 μg/日)の投与を目安とする。リン(Na_2HPO_4とNaH_2PO_4の混合)は1日4〜6回の分服が望ましく，リンとして30〜50 mg/kg/日(1〜3 g/日)の投与を目安とする。副作用をきたさないよう適宜投与量を調節することが重要である。治療によってくる病所見や血清ALP値の高値，成長速度は改善し，早期に治療を開始することでより良好な最終身長が得られる。しかし，血清リンや成長の正常化は困難である。リンの過剰投与による副甲状腺機能亢進症に注意が必要である。副甲状腺摘出の報告もある。下肢の変形が著明なときは，装具の装着や外科的な骨切り術を考慮する。活性型ビタミンD投与による高Ca血症，高Ca尿症，腎石灰化に十分注意する。腎エコー上腎石灰化がよくみられるが，腎機能障害をきたすことはまれである。成人期の治療効果については評価が定まっていない。不全骨折や骨痛などの症状のある成人に対しては治療すべきであるという意見がある。成長ホルモンの成長障害に対する効果が報告されているが，最終身長への効果は明らかではない。

Key Words: くる病，低リン血症，X連鎖性低リン血症性くる病，FGF23

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特　集　軽症あるいは軽度小児内分泌疾患の定義と治療適応・治療戦略

軽度ビタミンD欠乏症

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はじめに

ビタミンDは20世紀初めにくる病を治癒する栄養因子として発見された．ビタミンDは食事から摂取されるだけでなく，ビタミンとしては例外的に，皮膚において紫外線照射により生合成される．その後，肝臓において25位水酸化ビタミンD(25OHD)に変換され，さらに腎臓の近位尿細管において1α,25位水酸化ビタミンD(1α,25(OH)$_2$D)に変換され，活性型となる．1,25(OH)$_2$Dは標的臓器にあるビタミンD受容体に結合し，標的遺伝子の転写を調節するホルモンとして作用する．特に，小腸におけるカルシウムやリンの吸収，骨における石灰化の促進，副甲状腺における副甲状腺ホルモン(PTH)の分泌抑制などの作用を発揮することで，ビタミンDは体内のCa(カルシウム)やP(リン)の恒常性を維持し，骨の成長と石灰化に重要な役割を担っている．また，血中25OHD濃度は体内のビタミンDの貯蔵量を反映するので，ビタミンD欠乏症の診断に用いられる．本項ではビタミンD欠乏症と共に軽度ビタミンD欠乏症について述べる．

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1 ビタミンD欠乏症の定義

ビタミンD欠乏症は骨・軟骨の石灰化障害によって引き起こされる骨変形や成長障害，低Ca血症によるテタニーや痙攣を呈する．骨・軟骨の石灰化障害が成長軟骨帯の閉鎖以前に発症した場合くる病と呼ばれ，成長軟骨帯の閉鎖後の成人においては骨軟化症と呼ばれる．ビタミンD欠乏の診断は血中25OHD濃度によって行われる．しかし，日本では保険適応がないことが問題である．多くの検査室では血清25OHD値の基準値の下限が10ng/ml程度であるが，成人において，血中25OHD濃度が20ng/ml(50nmol/l)以下をビタミンD欠乏，30ng/ml(75nmol/l)以下をビタミンD不足とする場合が多いが，今だ議論がある[1〜3]．小児も同様の基準を適応すると考える傾向にある[3,4]．

2 軽度(潜在性)ビタミンD欠乏症の定義

軽度(潜在性)ビタミンD欠乏症の定義は一般的には明らかではない．私見ながら，血中25OHD濃度の低下(20ng/ml以下)を認め，かつ血清カルシウム値もしくは血清リン値の低下と，血中PTH濃度の増加が見られるが，臨床症状やレントゲン上の異常を認めない症例が「潜在性ビタミンD欠乏症」と筆者らは考える．つまり，この「潜在性ビタミンD欠乏症」は，ビタミンD欠乏により血液生化学的な異常が見られるが，テタニーや骨・軟骨の石灰化障害に至っていない症例と考える．「潜

表　ビタミンD欠乏症の段階的分類

Stage	血清Ca	血清P	PTH	1α,25(OH)$_2$D
I	L	N	N-H	N-H
II	N	L	H	H
III	L	L	H	L-N-H

L, 低値；N, 基準値内；H, 高値. 文献4, 6より改変.

在性ビタミンD欠乏症」は基本的には採血などで偶発的に見つかる症例である.

3 ビタミンD欠乏症の病態

ビタミンD欠乏の主要な要因の一つはビタミンDの摂取不足である. 日本の2010年版の食事摂取基準[5]によると, ビタミンD摂取の目安量は6カ月未満が100単位 (2.5μg), 6カ月から1歳未満が200単位, 1－7歳が100単位, 8－9歳が120単位, 9－14歳が140単位, 15－17歳が180単位, 18歳以上が220単位となっている. ただし, 日照を受ける機会が少ない乳児における目安量は200単位に増量されている. ビタミンDが多く含んだ食品として, 魚介類, 卵黄, バター, キノコ類などがある. 一方, 2011年の米国のInstitute of Medicine (IOM) の報告[1]においては, ビタミンD推奨量は1歳未満が400単位, 1－70歳が600単位, 71歳以上が800単位と日本より多い量になっている. ビタミンDは皮膚において紫外線照射によって合成されるため, 日光照射が不足するとビタミンD欠乏になり得るが, 皮膚に悪影響を与えずにビタミンDを十分に供給できる日光照射量が不明であるとして, 必要な日光照射量は明示されていない[1]. ビタミンD欠乏の危険因子として, 完全母乳栄養や母体のビタミンD摂取不足, アレルギーなどによる食事制限, 慢性下痢, 外出不足, 高緯度地域での居住, サンスクリーンの使用などが挙げられる.

ビタミンD欠乏では十分な量のCaとPが骨や軟骨に供給されないため, くる病や骨軟化症を呈する. また低Ca血症によるテタニーや痙攣も呈する. くる病や骨軟化症とは骨の石灰化が障害されたために石灰化されていない骨基質(類骨)が増加した状態である. さらに, くる病では成長軟骨帯の石灰化が障害される. 通常, 成長軟骨帯においては, 規則正しく分化した軟骨細胞が石灰化軟骨となり, 最終的には骨に置換される. しかし, くる病では, 成長軟骨帯における石灰化過程が障害されるため, 石灰化前線が乱れ骨X線上不整な骨端線が認められる.

4 ビタミンD欠乏症の症状

ビタミンD欠乏性くる病の症状としては成長板周囲の腫脹が多く, 手関節や足関節, 肋骨肋軟骨移行部 (肋骨念珠) によく見られる. 大きな大泉門, 前額部の突出, 頭蓋ろう, 歯芽崩出遅延, 歯のエナメル形成障害, 筋力低下, 筋緊張の低下が見られることもある. X線上のくる病所見として, 長管骨骨幹端では骨端線の拡大, 盃状陥凹, 毛羽立ちなどが見られる. 手関節や膝関節, 足関節に変化が現れやすい. ビタミンD欠乏性低Ca血症の症状としてテタニーや痙攣が見られる. ビタミンD欠乏症の臨床検査として, 低Ca血症, 低P血症, 高アルカリホスファターゼ血症, 血中25OHD値の低値, 血中PTH値の高値, 尿中Ca排泄の低下が認められる. しかし, 低Ca血症と低P血症の一方だけを認める場合がある[4,6] (表). 乳児期早期において, 血清P値は低値でないことが多く, 低Ca血症によるテタニーや痙攣が見られやすい (stage I). 乳児期後期や幼児期には, 血清Ca値は正常下限に保たれるが血清リン値は低値となり, 骨X線上くる病所見が見られるようになる (stage II). 歩行開始後はO脚や動揺性歩行が見られる. さらに血清Ca値も維持できなくなり,

血清Ca値，P値ともに低値となる（stage Ⅲ）．血中1,25(OH)$_2$D値はビタミンD欠乏の指標にならないことに注意する．思春期の成長著しい時期においてもビタミンD欠乏が比較的現れやすい．

5 潜在性ビタミンD欠乏症の治療適応

潜在性ビタミンD欠乏症が無治療で経過すれば，臨床症状やレントゲン異常を伴うビタミンD欠乏症が顕在化すると考えられるため，ビタミンD欠乏の明らかな血液生化学的な異常を認めれば，治療の適応と考える．

6 潜在性ビタミンD欠乏症の治療戦略

ビタミンD欠乏症（顕在性）において，我が国ではビタミンDが処方できないため，アルファカルシドール（1αOHD）約0.1μg/kg/day（1.0－4.0μg/day）が使用され，血液検査の改善と共に減量する．まず，PTHを正常化することを治療目標とする．潜在性ビタミンD欠乏症におけるアルファカルシドールの初期投与量は顕在性ビタミンD欠乏症と同様でよいと考えるが，血液生化学検査所見の異常が顕著でなければ初期投与量を減少する．血液検査所見の異常が軽微であれば，サプルメントとしてのビタミンDの補充で治療可能な症例もある．アルファカルシドールの過剰投与による高Ca血症や腎石灰沈着症のリスクとなる高Ca尿症をきたさないように注意しながら，投与量を調節する．また，Ca摂取が不足している場合はCaも投与する．典型的には血液所見は速やかに改善し，くる病変化も6カ月以内に改善してくる．上記治療にて改善傾向が乏しければ診断を再考する．痙攣を伴う低Ca血症の場合，心拍数の変化に注意しながらCa製剤を緩徐に静注し血清Ca値を補正する．

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特　集　小児内分泌学の進歩2011

低フォスファターゼ症の一部は低身長の精査を契機に診断される

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はじめに

低フォスファターゼ症は組織非特異的アルカリフォスファターゼ（Tissue nonspecific alkaline phosphatase：以下TNSALP）の活性低下により，全身の骨化障害や骨変形をきたす遺伝性疾患である．本症の症状のスペクトラムは広く，骨化障害や骨変形をほとんど認めない症例も存在する．

今回，低身長を主訴に当科を受診し，その精査の過程で本症の診断に至った2例を経験した．本症例のように骨症状が目立たない症例においては，低身長精査が診断の契機となる可能性があり，注意が必要と考えられた．

1 症　例

症例1　3歳4カ月，男児．

主　訴　低身長．

出生歴　在胎37週6日，体重2370 g，身長48.0 cm，頭位自然分娩で出生した．

家族歴　父の身長は170 cm，母の身長は163 cm，Target Heightは173.0 cmであった．また，家族内に骨系統疾患を指摘されている者はいない．

現病歴　生後1カ月時に両前腕・下腿の彎曲を主訴に整形外科を受診した．その際Campomelic dysplasiaをはじめとする骨系統疾患を疑われたが，*SOX9*遺伝子異常などは認めず，その後の経過観察で骨所見は改善傾向となっていた．1歳を過ぎた頃より低身長を認め，徐々に進行していた．今回，低身長を主訴に当科へ紹介受診となった．

現　症　84.8 cm（－3.03 SD）の低身長を認めた（**図1左**）．また，骨年齢は原法RUSで2.9歳であった．均整のとれた体格で，arm spanは82 cmと正常範囲内であった．外見上，骨系統疾患は否定的と考えられたが，下腿に計3カ所のdimpleを認めていた．

各種検査所見　当科受診時の両下肢X線写真を示す（**図2**）．生後4カ月時に整形外科を受診した際には下肢の彎曲を認めていたが，当科を受診した3歳時には明らかに改善していたため，画像所見から骨系統疾患を疑うことは困難であった．カルシウム代謝関連検査（**表1**）では，血清アルカリフォスファターゼ（以下ALP）値が112 IU/lと低値であった．また，尿中アミノ酸分析（**表1**）でフォスフォエタノールアミン（Phosphoethanolamine：以下PEA）が著明に上昇しており，低フォスファターゼ症が疑われた．なお，血漿IGF-I値は正常範囲内であった．低フォス

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[*4] 大阪大学大学院医学系研究科小児科学
Tomotaka Kono：Short stature is one of the key findings in mild type of hypophosphatasia.
Division of Endocrinology and Metabolism, Saitama Children's Medical Center.

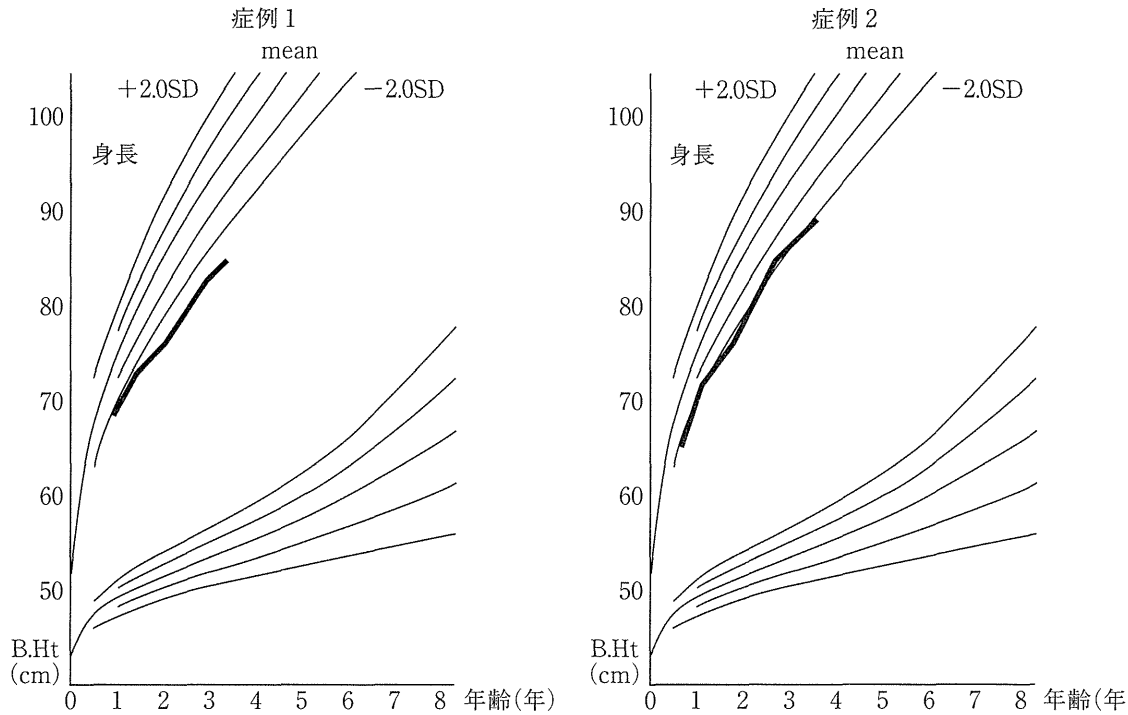


図1　成長曲線（左；症例1，右；症例2）

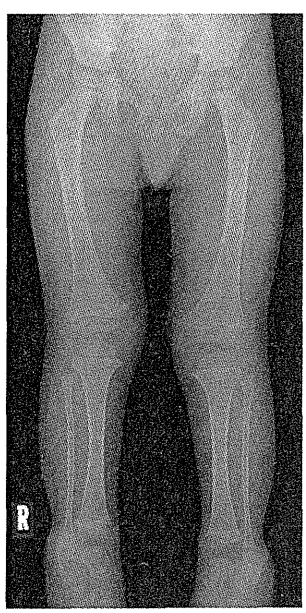


図2　両下肢X線写真（症例1）
3歳4カ月時．全身骨X線写真に異常はなかった．乳児期にみられていた下腿の彎曲は改善していた．

ファターゼ症の原因遺伝子である*TNSALP*遺伝子解析を施行したところ，F310L/G322Rの複合ヘテロ接合性変異を同定した（**表1**）．

症例2　3歳7カ月，男児．

主　訴　低身長．

出生歴　在胎38週3日，体重2946 g，身長50.0 cm，頭位自然分娩で出生した．

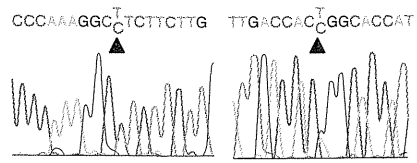
家族歴　父の身長は160 cm，母の身長は154 cm，Target Heightは163.5 cmであった．また，家族内に骨系統疾患を指摘されている者はいない．

現病歴　生後9カ月時に低身長（65.0 cm，−2.72 SD）を主訴に当科を受診した．その際，内分泌学的基礎値に異常はなく，身長も成長曲線に沿って伸びていたため，経過観察となっていた．2歳の終わり頃より乳歯の早期脱落を認め，歯科受診をしていたことから，低身長を含めて再度精査を行った．

現　症　89.3 cm（−2.22 SD）の低身長を認めた（**図1右**）．また，骨年齢は原法RUSで2.6歳

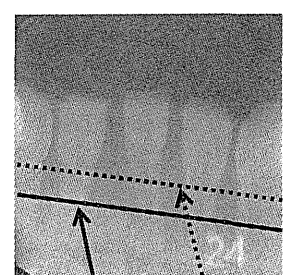
表1 症例1（各種検査所見）

カルシウム代謝関連検査			
Ca	9.5 mg/dl	P	6.3 mg/dl
ALP	112 IU/l	BAP	8.3 μg/l
I-PTH	18.6 pg/ml	HS-PTH	50.0 pg/ml
25(OH)D	22.0 ng/ml	1-25(OH)$_2$D$_3$	49.0 pg/ml
尿中アミノ酸分析：Phosphoethanolamine		208.6 nmol/mg・Cr	



F310L G322R

TNSALP 遺伝子解析結果
F310L/G322R
(compound heterozygote)



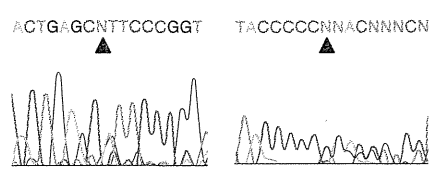
健常児の歯槽骨のライン

症例2の歯槽骨のライン

図3 歯槽骨X線写真（症例2）
3歳7カ月時．全身骨X線写真に異常はなかった．歯槽骨上縁が健常児と比較して下方に存在する．

表2 症例2（各種検査所見）

カルシウム代謝関連検査			
Ca	10.1 mg/dl	P	6.1 mg/dl
ALP	157 IU/l	BAP	9.9 μg/l
I-PTH	16.6 pg/ml	HS-PTH	50.0＞pg/ml
25(OH)D	35.1 ng/ml	1-25(OH)$_2$D$_3$	50.0 pg/ml
尿中アミノ酸分析：Phosphoethanolamine		1853.2 nmol/mg・Cr	



R119H 1559delT

TNSALP 遺伝子解析結果
R119H/1559delT
(compound heterozygote)

であった．外見上，四肢が短い印象があったため，arm span を測定したところ 82.0 cm と上肢の短縮を認めた．

各種検査所見　全身骨 X 線写真では骨系統疾患を疑わせる所見は認めなかった．しかし，歯科で撮影した歯槽骨 X 線写真（**図 3**）では歯槽骨上縁が健常児と比較して下方にあり，乳歯の早期脱落の原因と考えられ，何らかの骨系統疾患が疑われた．カルシウム代謝関連検査（**表 2**）では，血清 ALP 値が 137 IU/l と低値であった．尿中アミノ酸分析（**表 2**）では PEA が著明に上昇していたため，低フォスファターゼ症が疑われた．なお血漿 IGF-I 値は正常範囲内であった．*TNSALP* 遺伝子解析を施行したところ R119H/1559delT の複合ヘテロ接合性変異を同定し，低フォスファターゼ症の確定診断に至った（**表 2**）．

2 考　　察

低フォスファターゼ症は，骨の低石灰化に基づく骨化障害・骨変形・乳歯の早期脱落などを主症状とする遺伝性疾患である．原因遺伝子は染色体 1p36.1-34 に座位する *TNSALP* 遺伝子で，通常は常染色体劣性遺伝形式を示すが，常染色体優性遺伝形式の症例もまれに存在する[1]．同遺伝子がコードする TNSALP の活性低下によって，血清 ALP 低値や骨石灰化異常をきたし，TNSALP の基質である PEA の尿中濃度が上昇することが特徴的である．現在までにおよそ 250 種類の同遺伝子変異が同定されている[2]．古典的な臨床病型としては，発症時期や症状に応じて，周産期型（perinatal type），乳児型（infantile type），小児型（childhood type），成人型（adult type），歯限局型（odonto type）の 5 型に分類されている．しかし，最近では必ずしもこの病型分類に当てはまらない症例も報告されており注目されている[3]．例えば，これまで最重症で致死的と考えられてきた周産期発症にも関わらず予後良好に経過している症例[4]や，出生時の骨症状が軽度で自然軽快を示した症例[5]など，本症の表現型は多彩であることが分かってきた．その表現型や重症度には TNSALP の残存酵素活性が関連すると考えられている[6]．

今回，当科受診時に骨化障害や骨変形をほとんど認めず，低身長が主症状であった低フォスファターゼ症を 2 例経験した．両症例とも臨床的には軽症であったことから，少なくとも一方のアリルの変異型には TNSALP 残存酵素活性が存在するものと推測された．症例 1 の F310L は日本人に多くみられ，残存酵素活性を有する変異型として知られている[4]．一方，症例 2 の 1559delT は日本人に多く見られる残存酵素活性のない変異型である[4]が，もう一方の R119H は Taillandier A ら

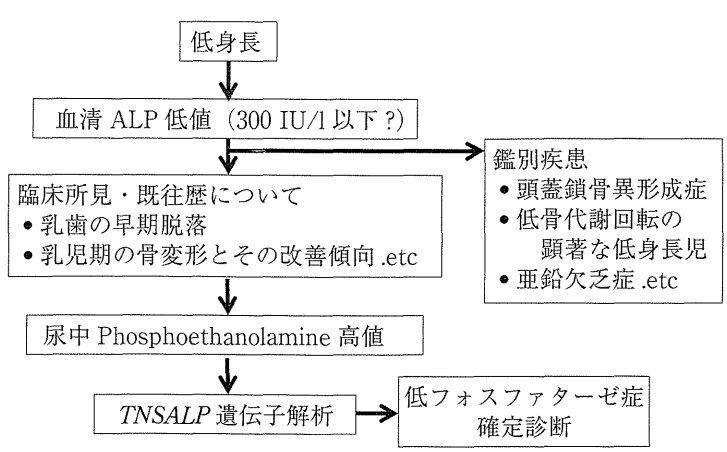


図 4　低身長精査時の低フォスファターゼ症診断のためのチャート

により，野生型と比較して33.4%の残存酵素活性を有する変異型として報告されている[7]．本症にはこのような軽症例が潜在的に存在している可能性があり注目される．

今回の経験から，低フォスファターゼ症の軽症例の中には骨変形などの特徴的症状を認めず，低身長を主訴に病院を受診し，その精査の過程で診断に至る症例が存在すると推測された．TNSALPノックアウトマウスでは，骨石灰化異常だけでなく，軟骨組織の分化異常によって成長軟骨帯の組織学的な構造変化をきたすとする報告もあることから，本症と低身長の関連性が示唆された[8]．

以上のことをふまえて，低身長精査時における低フォスファターゼ症診断のためのチャートの作成を試みた（**図4**）．一般血液生化学検査にて血清ALP低値（我々は300 IU/l以下と考えている）の際には，改めて臨床所見や既往歴などを確認する．乳歯の早期脱落や，乳児期の骨変形とその改善傾向などを認めていた場合には，尿中アミノ酸分析を追加する．その際，PEAの尿中濃度が高値であれば本症の可能性があるため，*TNSALP*遺伝子解析を施行することによって，本症と確定診断をすることが可能であると考えられた．

結　語

今回，骨化障害や骨変形をほとんど認めず，低身長精査の過程で診断に至った低フォスファターゼ症の2例を経験した．今回の経験から，ALPは骨石灰化に重要であるとともに，骨成長への関与が推測された．低身長の精査時には，低フォスファターゼ症の存在にも留意する必要があると考えられた．

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Pediatric Aspects of Skeletal Dysplasia

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Abstract

Skeletal dysplasia is a disorder of skeletal development characterized by abnormality in shape, length, a number and mineral density of the bone. Skeletal dysplasia is often associated with manifestation of other organs such as lung, brain and sensory systems. Skeletal dysplasias or dysostosis are classified with more than 400 different names. Enchondral bone formation is a coordinated event of chondrocyte proliferation, differentiation and exchange of terminally maturated chondrocyte with bone. Impaired enchondral bone formation will lead to skeletal dysplasia, especially associated with short long bones. Appropriate bone volume and mineral density are achieved by balance of bone formation and bone resorption and mineralization. The gene encoding fibroblast growth factor receptor 3 is responsible for achondroplasia, representative skeletal dysplasia with short stature. The treatment with growth hormone is approved for achondroplasia in Japan. Osteogenesis imperfecta is characterized by low bone mineral density and fragile bone. Data on the beneficial effect of bisphosphonate for osteogenesis imperfecta are accumulating. Osteopetrosis has high bone mineral density, but sometimes show bone fragility. In Japan as well as other countries, pediatrician treat larger numbers of patients with skeletal dysplasia with short stature and fragile bones compared to 20 years ago.

Ref: *Ped. Endocrinol. Rev. 2012;10(suppl 1):*

Key words: *Achondroplasia, Hypochondroplasia, Osteogenesis imperfecta, Osteopetrosis, Short stature, Fracture, Bone mineral density, Bisphosphonate*

Introduction

Skeletal dysplasia is a generic name for diseases accompanied by morphological changes and major lesions in the bones and cartilaginous tissues of patients (1). Skeletal dysplasia requires bone X-ray images for diagnosis (1, 2). While the prevalence of each disorder is rare, the prevalence of skeletal dysplasia in general is estimated at approximately one per several thousand. In the International Nomenclature and Classification, skeletal dysplasia is classified according to their similarity in etiologies and radiological findings. Since 1970, the number of target disorders has increased to 456 types in disease name that are classified into 40 categories (3). In addition, more than 200 responsible genes have been identified as a result of the development of molecular biology and genetics tests in recent years. As such, it is not easy to describe the historical background for each of these diseases. Accordingly, this review will chiefly discuss the representative cases of skeletal dysplasia associated with failure to thrive, short stature and susceptibility to fracture, which are often chief complaints of patients visiting a pediatrician, in light of the history in Japan.

Skeletal Dysplasia Associated with Failure to Thrive

Mechanism and abnormality of chondrocyte proliferation and differentiation

Chondrocytes in the growth cartilage area located at the metaphyseal region of long bones will proliferate and differentiate, and then will be replaced by bone (4). This mechanism, termed endochondral ossification, enables changes, such as limb lengthening, which allows a child to grow taller. Skeletal dysplasia associated with short stature is mostly associated with an abnormality in chondrocyte differentiation and proliferation. During endochondral ossification, chondrocytes in the growth cartilage area (growth plate) differentiate in order from resting chondrocytes to proliferating chondrocytes, prehypertrophic chondrocytes, hypertrophic chondrocytes, and finally to calcified cartilages (**Figure 1**) (5). Endochondral ossification progresses with the involvement of numerous transcription factors, growth factors, signaling molecules, extracellular matrix.

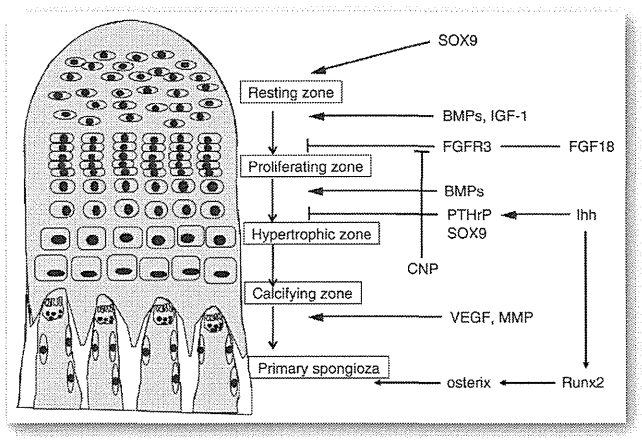

Figure 1. Molecules involved in endochondral bone formation.

Chondrocytes differentiate in order from the resting zone to the hypertrophic zone via the proliferating zone. The hypertrophic zone becomes calcified after infiltration of the blood vessel supply by vascular endothelial growth factor (VEGF) and degradation of the matrix by matrix metalloproteinases (MMP), and is absorbed by chondroclasts. Cartilage is finally replaced by primary bone spongiosa. Sox9 is the master gene of chondrocyte development and promotes chondrocyte differentiation from mesenchymal cells, while having an inhibitory effect on chondrocyte hypertrophy. Bone morphogenetic proteins (BMPs) and insulin-like growth factor-1 (IGF-1) stimulate the proliferation of chondrocytes. Fibroblast growth factor receptor 3 (FGFR3), together with FGF18, inhibits proliferation of chondrocytes. C-type natriuretic peptide (CNP) antagonizes the inhibitory effect of FGFR3. Indian hedgehog (ihh) induces parathyroid hormone-related peptide (PTHrP), which inhibits the hypertrophic differentiation of chondrocytes. Runx2 and osterix from osteoblasts promote bone formation (primary spongiosa).

The principal component of cartilage matrix will change from a matrix primarily made of type II collagen to type IX collagen, and finally type X collagen, with progressive enlargement of chondrocytes. The hypertrophic chondrocytes will then undergo apoptosis as the matrix undergoes calcification. The calcified cartilage matrix is then digested by proteases, such as matrix metalloproteinase (MMP) 9 and is absorbed by chondroclasts. It will be finally replaced by bone after infiltration of the vascular supply.

There are various skeletal dysplasia associated with abnormalities in chondrocyte differentiation. Campomelic dysplasia is caused by a mutation in SOX9, a gene essential for the induction of chondrocytes from mesenchymal tissues (6). Achondroplasia, on the other hand, stems from constitutive activation of the fibroblast growth factor receptor type 3 (FGFR3), which negatively controls chondrocyte proliferation (7, 8). An abnormality in cartilage-specific type II collagen is observed in spondyloepiphyseal dysplasia congenita, whereas an abnormality in type X collagen is observed in Schmid-type metaphyseal dysplasia (9); these abnormalities are collectively called collagenopathies (9). Spondyloepiphyseal dysplasia tarda is caused by altered cartilage formation resulting from mutations in the SEDL gene (10). If a short stature due to a shortened trunk, neck and limbs (dwarfism) is diagnosed in patients 8 years and older, presence of buffalo hump is determined using lateral spine radiographs. Important cartilage matrix component other than collagen is proteoglycan such as aggrecan. Other disorders, such as diastrophic dysplasia, achondrogenesis type 1B, atelosteogenesis type II, occur due to abnormalities in the DTDST (diastrophic dysplasia sulfate transporter) gene that transports sulfate into chondrocytes to maintain adequate levels of proteoglycan sulfation (11). Transient receptor potential vanilloid 4 (TRPV4) is a non-selective cation channel that passes calcium ions. Mutation of TRPV4 has led to a class of skeletal dysplasia known as the TRPV4 group. An increasing number of diseases have been revealed to belong to this group in recent years, including brachyolmia, spondylometaphyseal dysplasia Kozlowski type, metatropic dysplasia, spondyloepiphyseal dysplasia type Maroteaux, parastremmatic dysplasia, and familial digital arthropathy-brachydactyly partly thanks to the significant contribution of Japanese researchers (12).

Achondroplasia

Concept

Achondroplasia represents a collection of disorders, including hypochondroplasia, lethal bone dysplasia, and SADDAN (severe achondroplasia with developmental delay and acanthosis nigricans) syndrome, which arise due to constitutively active, ligand-independent mutations in FGFR3 gene leading to excessive downstream signaling (8, 13). Disorders belonging to the FGFR3 mutation family are mostly caused by de novo mutation and are inherited as an autosomal dominant trait. The accurate prevalence of patients with this mutation is unknown. The prevalence of achondroplasia is estimated at one per 15,000 to 30,000 newborns. In the United States, estimates put the prevalence of achondroplasia at one per 16,670 to 27,780 newborns (14).

Diagnosis and treatment

Patients with achondroplasia present with short stature, shortened limbs, abnormal facial features (prominent forehead, nasal root depression, mid-face hypoplasia, and mandibular protrusion), an enlarged head size, and trident hands. Patients also appear to have excessive amounts of soft tissue. In addition, their gluteal region protrudes backward with an increase in lumbar flexion, and they have failure in elbow joint extension (15). Tooth overcrowding and malocclusion are also problematic. In terms of short stature, patients with achondroplasia lack a pubertal growth spurt; thus their difference in stature as compared with normal individuals becomes increasingly significant with age. The average adult height for patients with achondroplasia is approximately 128-130 cm for males and approximately 120-125 cm for females according to data from the United States, Argentina, and Japan (16). Other probable issues include communicating hydrocephalus, foramen magnum stenosis, sleep apnea, otitis media, and spinal canal stenosis. Symptoms of nerve compression are also often noticed as constipation or an increased patellar tendon reflex. With a broad range of physical deformities, cooperation between neurosurgeons, orthopedists and otolaryngologists is important.

On plain X-rays, achondroplasia is characterized by thick and short long bones, metaphyseal cupping, bullet-shaped vertebra, fibula that are longer than the tibia, decreased distance of lumbar spine pedicles, a large cranial base yet with small facial bones, a small ischial notch, and a small cavity of the lesser pelvis. Flat vertebra may be observed in a newborn patient.

In terms of a genetic diagnosis, achondroplasia patients with FGFR3 gene mutation will show arginine substitution of glycine 380. In patients with the milder hypochondroplasia, FGFR3 mutations such as Ile538Val, Asn540Lys, and Asn540Thr have been reported.

In Japan, growth hormone treatment was approved in child patients with a short stature due to achondroplasia or hypochondroplasia (up to -3 SD) in 1997, and certain efficacy has been proven so far (17). The Foundation for Growth Science in Japan provides diagnostic support and organizes reports for side effects. The data on the efficacy of growth hormone treatment for adult height is expected to be organized soon. A clinical study is about to commence for a CNP (C-type natriuretic peptide) analogue developed as a drug after a Japanese group reported the efficacy of CNP in an animal model with achondroplasia (18).

Skeletal Dysplasia with Changes in Bone Volume

Mechanism leading to loss of bone volume

Bone volume is determined by the functional balance between osteoblasts and osteoclasts. Bone volume will increase with growth and bone formation surpasses bone resorption during the growth period and for several years after the cessation of growth (**Figure 2**). It is known that bone volume is affected by several environmental factors, such as polygenes, nutrition, and exercise (19).

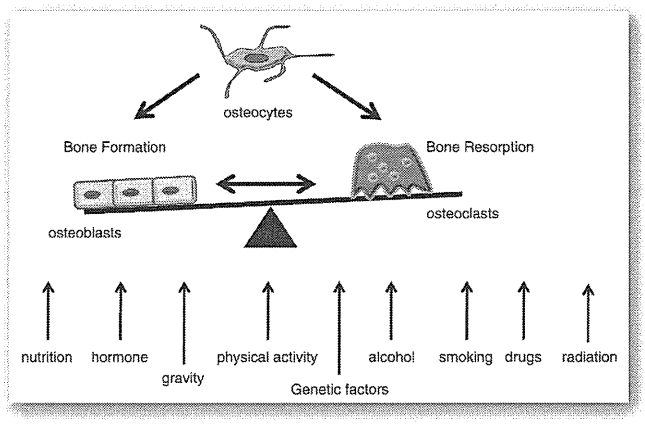

Figure 2. Bone volume determination.

Osteoporosis and osteopetrosis are disorders associated with low and high bone mass, respectively. Bone volume is determined by the balance of bone formation exerted by osteoblasts and bone resorption by osteoclasts. Osteocytes are the most abundant cells in bone and involved in controlling bone mass in response to various types of stimuli and phosphate homeostasis. Bone modeling is dominant during childhood, and bone formation slightly surpasses

bone resorption, thus leading to growth and the increase in bone volume. Several factors, such as nutrition and hormone levels, also affect peak bone mass.

Insufficiency fracture is nontraumatic fracture caused by a minor external force in areas where there is low bone volume (20). **Table 1** summarizes the hereditary diseases resulting in loss of bone volume. The bone matrix is primarily made up of type I collagen, and deposited crystal of calcium and phosphorus, termed hydroxyapatite. Type I collagen is the most abundant protein in bone matrix, consisting of two α1 chains and one α2 chain of different gene derivations. The combination of these three chains constitutes the formation of collagen fibers. Osteogenesis imperfecta derives from an abnormality in type I collagen production, and is characterized by an increased susceptibility to fracture due to a loss of bone strength.

Type	OMIM	Severity	Clinical symptoms	Inheritance	Gene
I	166200	mild	Blue sclera, fragility, deafness	AD	COL1A1, COL1A2
II	166210	lethal	Short-limb, soft skull, narrow chest, thin or wide rib, blue sclera	AD, AR	COL1A1, COL1A2
III	259420	severe	Blue sclera in infancy, fragility, progressive bone deformity, dentinogenesis imperfecta	AD	COL1A1, COL1A2
IV	166220	mild with bone deformity	White sclera, dentinogenesis imperfecta, mild short stature	AD	COL1A1, COL1A2
V	610967	moderate, severe	Hypercallus formation, calcification, swelling	AD	?
VI	613982	moderate, severe	Bone deformity, blue or grayish sclera, mineralization defect	AR	SERPNF1
VII	610682	moderate	Blue sclera, rhizomelic short limb	AR	CRTAP
VIII	610915	severe	Short-limb, soft skull, white sclera, barrel-shaped chest	AR	LEPRE1
IX	259440	moderate, severe	Bone deformity, kyphoscoliosis, joint hypermobility	AR	PPIB
X	613848	various	Blue sclera, short limb, bone deformity	AR	SERPINH2
XI	610968	moderate, severe	Contracture, webbing (Bruck syndrome)	AR	FKBP10
XII	613849	moderate	Normal sclera, mild bone deformities	AR	SP7

AD=autosomal dominant, AR=autosomal recessive

Table 1. Classification of osteogenesis imperfecta.

Osteogenesis Imperfecta (OI)

Concept

OI is characterized by such symptoms as susceptibility to fracture and decreased bone density due to loss of bone strength. It results from abnormality in type I collagen (α1 or α2 protein chains), encoded by COL1A1 and COL1A2 genes. Sillence initially classified this disorder into four types (21); however, a detailed study on gene abnormalities from bone biopsies led Glorieux *et al.* to classify OI into seven types (22). The number of disease types has increased because an increasing number of causative genes are identified (**Table 1**) (23, 24). Type I is classified as mild, without bone deformation and with blue sclera, and approximately one-half of the cases are associated with deafness. Type II is a perinatal lethal form, from which most patients die from respiratory failure early after birth. Type III is a severe form, and most patients cannot walk on their own due to progressive bone deformity resulting from frequent fracture. Type IV has an intermediate severity between Type I and Type III and presents with bone deformity and short stature. It is divided into A (with) and B (without) subtypes, according to presence or absence of dentinogenesis imperfecta. Dentinogenesis imperfecta is characterized by change in tooth color, from light yellow to brown, a loss of luster, and dentin exposure due to insufficient enamel formation. It is mostly inherited as an autosomal dominant trait. Part of the disease type can be caused by enzyme abnormality, and is then inherited as an autosomal recessive trait.

As collagen chains start integrating from the C terminus, mutated collagens will not be incorporated into the collagen

fibers if there is interference due to the presence of an interrupting stop codon, for instance. In this case, OI is mostly found as Type I, with mild severity. On the other hand, if a glycine is mutated, OI is considered to be severe because the abnormal collagen destroys the structure of the normal collagen fibers (25).

Diagnosis and treatment

Symptoms such as susceptibility to fracture and radiological findings are used as the basis for diagnosis. In radiological findings, as the disease progresses, thinning of the cortical bone is easy to determine. In patients with OI Type II, there is obvious deformity and disruption in the unity of the cranial bone. Long bone deformity due to frequent fracture is also apparent as light and shade banding along the bone, almost in an accordion-like manner. In OI Type III, irregular swelling is observed as a 'popcorn-like' appearance in the metaphysis. Wormian bones, or extra sutural bones, are also found in the cranium.

OI can also be diagnosed genetically. More than 300 mutations have been reported (http: //www.le.ac.uk/genetics/collagen/index.html). In approximately 90% of OI patients, mutation is found either in COL1A1 (17q21.31-q22), which encodes the α1 chain, or COL1A2 (7q22.1), which encodes the α2 chain. Recently, a mutation of the CRTAP gene, which encodes the cartilage associated protein (CASP or CRTAP) required for prolyl 3-hydroxylation, was reported as a causative gene for OI in an autosomal recessive genetic form (23, 24). In addition, new genes involved in the onset of OI are continuously being identified, such as leucine proline-enriched proteoglycan (leprecan) 1 (LEPRE1), peptidylprolyl isomerase B (PPIB), FK506 binding protein 10 (FKBP10), SERPINH1 (which encodes the collagen chaperone-like protein, HSP47), osterix (Sp7), procollagen-lysine, 2-oxoglutarate 5-dioxygenase 2 (PLOD2), and SERPINF1 (which encodes pigment epithelium-derived factor) (**Table 1**) (23,24). A recent study has reported OI caused by BMP1/mTLD, a procollagen I C-terminal propeptide (PICP) endopeptidase gene (26).

Intravenous pamidronate treatment has been reported for OI targeting patient susceptibility to fracture and low bone mineral density (22). The Japan Endocrine Society prepared the "Clinical Practice Guidelines on Osteogenesis Imperfecta" in 2006 for procedures using this treatment. In their assessment of bone tissue images, it was reported that pamidronate treatment thickened the width of the cortical bone, which likely resulted in the increase in the bone strength and the increase in bone mineral density. Pamidronate treatment also increases the percentage of cancellous or spongy bone. While early treatment is expected to result in improved outcomes for OI patients, bisphosphonate treatment has side effects, and thus care should be taken when choosing pamidronate as a treatment strategy in mild OI patients (27). Treatment with intramedullary nailing and orthoses should also be used in patients who experience frequent fracture and deformity.

Osteoporosis-pseudoglioma Syndrome (OPPG)

Concept

OPPG is a disorder characterized by severe childhood osteoporosis and congenital or juvenile blindness. Patients suffer from frequent fractures during childhood due to an increased susceptibility to fracture, and are later confined to a wheelchair due to bone ache, spinal column curvature, bone deformity, among other causes. OPPG is a rare disorder with an autosomal recessive trait caused by loss-of-function mutation of the LRP5 gene (low density lipoprotein receptor-related protein 5) located at 11q13.4 (28). The frequency of onset is estimated at one per 2 million, whereas the frequency of carriers with LRP5 gene mutation is estimated at one per 380,000 to 700,000, including people in the Japanese population (29).

In light of the fact that a loss of bone volume was not observed in osteoblast-specific LRP5 gene knockout mice, Karsenty *et al.* implemented a functional analysis of LRP5, and reported that bone volume is maintained by cancelling the action of serotonin of inhibiting osteoblast proliferation through the inhibition of serotonin synthase by the LRP5 in the intestinal tract (30). Future elucidation is expected in relation to serotonin and bone metabolism.

LRP6 is highly homologous to LRP5 and acts as a Wnt co-receptor, similar to LRP5. A spontaneous mutation in Lrp6 is responsible for ringelschwanz (rs) mice, which manifest with spina bifida and low bone mineral density. This indicates that LRP6 is important for skeletal formation and bone metabolism (31). Interestingly, the rs mice showed a loss in bone volume due to increased bone resorption in association with an increased expression of RANKL, with no abnormality in osteogenesis; this indicates a functional difference from LRP5. This gene mutation in LRP6 has also been identified in a human family, with all members displaying evidence of early coronary disease, hyperlipemia, hypertension, diabetes and osteoporosis (32).

Diagnosis and treatment

The presence of mutations of the LRP5 gene is confirmed, along with the appearance of any osteoporotic changes. Furthermore, congenital or juvenile blindness serves as a clue to the disease.

Disorders Associated with Osteosclerosis

Mechanism of osteosclerosis

Osteoclasts are derived from hematopoietic stem cells, whose differentiation, activation, and existence involve many molecular groups. Mature osteoclasts are polarized and adhere to bones via integrins. The plasma membrane inside the bone adhesion site forms a ruffled border. In this resorption cavity, cathepsin K (lysosomal enzyme) and acids are secreted to resorb bones actively (**Figure 3**). Abnormality in the production or secretory process of these enzyme and acids interfere with bone resorption to induce osteosclerotic disorders represented by osteopetrosis (33).

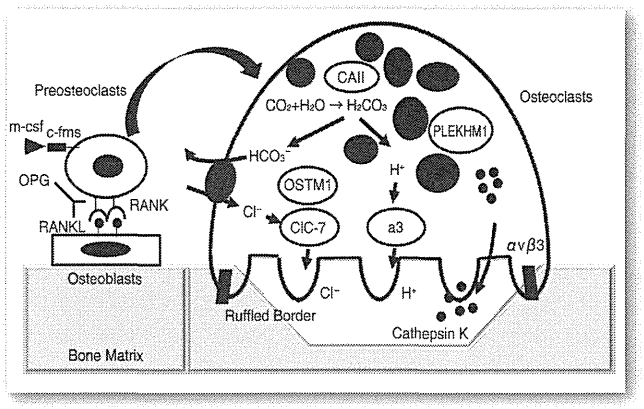

Figure 3. Osteoclasts.

The figure illustrates molecules involved in osteoclast formation and bone resorption. Mononuclear preosteoclasts, derived from hematopoietic stem cells, differentiate into multinuclear giant cells, termed osteoclasts, by the activity of Receptor activator of nuclear factor kappa-B ligand (RANKL) and macrophage colony stimulating factor (m-CSF). RANK and c-fms are their receptors, respectively. Osteoprotegerin (OPG) is a decoy receptor which prevents the interaction between RANKL and RANK. Osteoclasts have a unique structure, ruffled border, and excrete acid (H^+) with Cl^- and cathepsin K, both of which are essential to bone resorption. Carbonic anhydrase produces H^+, a protein called osteopetrosis-associated transmembrane protein 1 (OSTM1) and the chloride channel, CLC-7 provide the source of Cl^-. PLEKHM1 (pleckstrin homology domain containing, family M (with RUN domain) member 1) is involved in vesicular transport within osteoclasts. Disrupted function in any of these molecules can lead to osteopetrosis.

Disorders associated with osteosclerosis are largely divided into those with decreased bone resorption and those with increased osteogenesis. Osteopetrosis is a representative hereditary osteosclerotic disorder associated with bone resorption. In recent years, many genes responsible for this disorder have been identified (33). On the other hand, several constitutive genes for the Wnt signaling pathway have been identified as molecules responsible for osteosclerotic disorders associated with increased osteogenesis, and the importance of the Wnt signaling in the bone volume control came to be recognized (34,35). Other osteosclerotic disorders associated with increased osteogenesis include Camurati-Engelmann disease, osteopoikilosis, van Buchem disease, sclerosteosis, and endosteal hyperostosis (Worth type), which are not dealt with in this report.

Autosomal recessive infantile osteopetrosis

Autosomal recessive infantile osteopetrosis, also known as infantile malignant osteopetrosis for its poor outcome, occurs during early infancy with macrocephaly, progressive nerve deafness, blurred vision, hepatosplenomegaly, and/or severe anemia. Patients with this disorder present with diffuse osteosclerosis and are impaired both in bone modeling and remodeling. Deafness and blurred vision appear as symptoms of nerve compression due to narrowing of the neural tube, and anemia is caused by narrowing of the bone marrow cavity. Patients are vulnerable to infection and bleeding due to pancytopenia and mostly die before childhood, unless early treatment intervention occurs, such as hematopoietic stem cell transplantation (36).

To date, five genes have been linked to infantile osteopetrosis: TCIRG1, which encodes the vacuolar proton pump a3 subunit; CLCN7, which encodes the chloride channel; OSTM1, which is a human orthologue equivalent of the mouse grey-lethal gene; TNFSF11, which encodes RANKL; and TNFRSF11A, which encodes RANK (37-42). While the number of osteoclasts with impaired function increases in most disorders, the number of osteoclasts can also decrease in some disorders (43).

Autosomal dominant adult (late-onset) osteopetrosis

Autosomal dominant adult osteopetrosis (ADO) occurs more frequently and with milder severity than autosomal recessive infantile osteopetrosis. As such, these adult patients often asymptomatic and therefore remain undiagnosed. This disease has been classified into Type I (ADO I) and Type II (ADO II), according to the difference in radiological findings.

Patients with ADO I show significant sclerosis, especially in the cranial base, cortical thickening of the long bones, but little abnormality in the vertebral bodies (**Figure 4A**). It mostly remains asymptomatic, with a low fracture

frequency. In 2003, this disease type was classified as OPTA1 (osteopetrosis, autosomal dominant 1) following identification of LRP5 as the gene responsible for this disorder (44). Interestingly, this disease type is not a disorder of osteoclastic resorption, but osteosclerosis due to an abnormality in osteoblast function. Accordingly, this disease type does not fall under osteopetrosis in terms of its molecular pathogenesis.

ADO II is caused by heterozygous mutation of the CLCN7 gene, and is now referred to as osteopetrosis, autosomal dominant 2, or OPTA2 (45). In radiological findings of ADO II, osteosclerosis is observed in the whole body, with a significant increase in sclerosis in the cranial base. In addition, sclerosis of the vertebral body end plate observed as 'rugger-jersey' vertebra is observed in almost all patients (**Figure 4B**). Further, the long bones are recognized radiologically as 'bone within a bone', usually picked up during childhood in relation with a fracture, or osteomyelitis of the mandible, facial palsy, etc. Patients are more susceptible to fracture, as the immature bones are not replaced by mature compact bones due to impaired bone resorption.

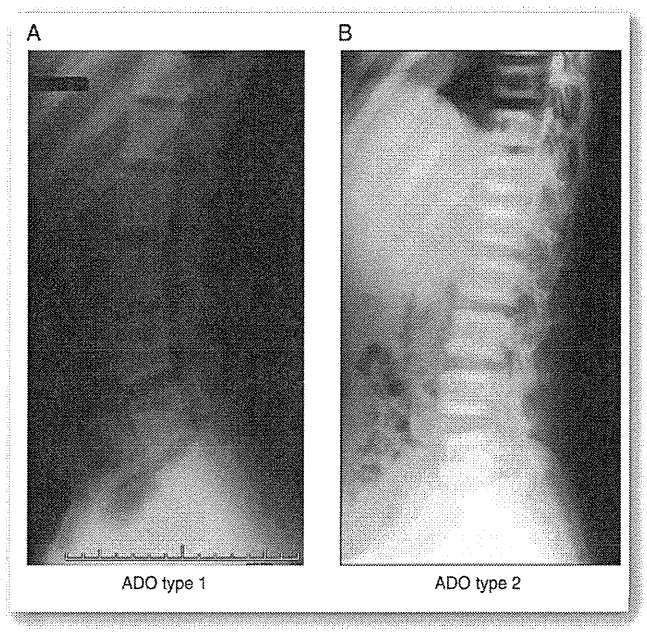

Figure 4. *(A) In autosomal dominant osteopetrosis (ADO) type I, high bone mass is apparent in base of the skull and no finding in the 'rugger-jersey' vertebra of the spine. In the patient, a heterozygous mutation (p.A214T) in the LRP5 gene was identified. (B) ADO type II is caused by mutations in the chloride channel gene, CLCN7. The heterozygous loss of CLCN7 impairs the function of osteoclasts. The heterozygous mutation, p.R286Q, was found in the patient. Rugger-jersey vertebra was also characteristic. In the laboratory examination, aspartate aminotransferase (AST), creatine kinase brain isoenzyme (CK-BB) and tartrate resistant acid phosphatase (TRACP)-5b were elevated.*

Intermediate Osteopetrosis

Intermediate osteopetrosis occurs during childhood with such symptoms as fracture, osteomyelitis, short stature, mild-to-moderate anemia, extra-medullary hematopoiesis, dental abnormality, facial palsy, and deafness with various degrees of severity. It is differentiated from infantile osteopetrosis by a better vital prognosis. This disease type stems from mutations to both alleles of the CLCN7 gene. In addition, in 2007, the PLEKHM1 (Pleckstrin homology domain containing, family M member 1) was also been identified as one of responsible genes for intermediate osteopetrosis, and the disease type was classified as osteopetrosis, autosomal recessive 6 (OPTB6) (46).

Other Osteopetrosis and Pycno-osteogenesis Imperfecta

Carbonic anhydrase II (CAII) is an enzyme highly expressed in osteoclasts and is involved in production of H_2CO_3, which is involved in bone resorption through its degradation to H^+ and HCO_3^-. Mutation of the CA2 gene, which encodes this enzyme, causes intermediate osteopetrosis in an autosomal recessive trait, since termed osteopetrosis, autosomal recessive 3 (OPTB3). This disease type presents with brain sclerosis and renal tubular acidosis, as well as osteopetrosis.

OLEDAID (ectodermal dysplasia, anhidrotic, with immunodeficiency, osteopetrosis and lymphedema) 14, is a new syndrome, advocated by Döffinger *et al.* in 2001, that presents with osteopetrosis, lymphatic edema, and EDA (ectodermal dysplasia associated with anhidrosis). These patients generally die during childhood from multiple infections. It is inherited as an X-linked recessive trait, and is caused by impairment to the NF-κB signaling pathway due to mutations in the IKBKG gene that encodes the nuclear factor κB (NF-κB) essential modulator (NEMO) (47).

Pycnodysostosis is an autosomal recessive hereditary disease that presents with short-limb dwarfism, cranial/facial dysplasia (enlargement of the anterior fontanel, enlargement of the cranial suture, maxillary/mandibular dysplasia, etc.), tooth dysplasia (delayed tooth eruption, abnormal arrangement of the teeth, etc.) and susceptibility to fracture, and is caused by loss-of-function mutation of cathepsin K (48).

Conclusion

The field of skeletal dysplasia is rapidly progressing, and pediatricians should be positively involved in the medical care of children with skeletal dysplasia with due understanding of the disorders. In Japan in particular, physicians should communicate with each other positive

results and pertinent information, such as improvements in adult height in patients with achondroplasia/ hypochondroplasia due to growth hormone treatment.

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Original Article

Treatment of Hypophosphatemic Rickets with Phosphate and Active Vitamin D in Japan: A Questionnaire-based Survey

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Abstract. Hereditary hypophosphatemic rickets represented by X-linked hypophosphatemic rickets (XLH) is a rare disorder characterized by hypophosphatemia, elevated alkaline phosphatase (ALP) and undermineralization of bone. Active vitamin D and phosphate are administered to correct hypophosphatemia and elevation of ALP. Overtreatment with phosphate leads to secondary hyperparathyroidism, and a large dose of active vitamin D has a risk of hypercalciuria. To understand the situation concerning treatment of patients with hereditary hypophosphatemic rickets in Japan, we conducted a questionnaire survey of pediatric endocrinologists. Answers were obtained from 53 out of 68 hospitals where the pediatric endocrinologists worked. One hundred and thirty-five patients were treated in 28 hospitals during November 2009 and May 2010; 126 patients suffered from hereditary hypophosphatemic rickets, and 9 had hypophosphatemia caused by other miscellaneous reasons. The distribution of patient age was as follows: 27 (21%) were between 6 mo and 6 yr of age, 39 (31%) were between 6 and 12 yr of age, and 60 (48%) were more than 12 yr of age. Active vitamin D was given to 123 patients, and phosphate was given to 106 patients. As for the dose of phosphorus, 37.2–58.1 mg/kg/d was given divided into 2 to 6 aliquots. There were various control targets of treatment, including serum phosphate, serum ALP, rachitic change, urinary Ca/Cr, parathyroid hormone and growth. It is very important to avoid side effects of these treatments. No evidence is available about the optimal dose of phosphate or number of administrations in the treatment of patients with hypophosphatemic rickets. Although there is a recommendation for clinical management of patients with hypophosphatemic rickets, we should set a clinical guideline for it in Japan.

Key words: hypophosphatemia, phosphaturia, rickets, active vitamin D, phosphate

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Introduction

Rickets is a disorder of calcification in chondrocytes and bone characterized by accumulation of unmineralized bone, termed osteoid. Characteristic X-ray findings such as cupping, flaring, and fraying strongly suggest