GROWTH FAILURE ASSOCIATED WITH SKELETAL DISORDERS

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INTRODUCTION

Skeletal disorders are a heterogeneous group of disorders, which result in disproportionate short stature. In an attempt to develop uniformity, an international nomenclature and classification was proposed in 1969 (1), originally called “Constitutional Disorders of Bone,” which was subsequently updated numerous times as knowledge of the molecular basis of disorders increased. In the 1992 revision, the classification was based on radiodiagnostic and morphologic criteria. In the 1997 revision, (2) the families of disorders were rearranged based on etiopathogenetic information regarding the gene and/or protein defect in these disorders. In the 2001 revision, the dysostoses were incorporated in the Nomenclature (3). Another molecular-pathogenetic classification of genetic disorders of the skeleton was also proposed in 2002 (4) (Table 1). Finally, the Nosology Group of the International Skeletal Dysplasia Society was recently formed in order to cope with the increasing complexity of information. They developed the 2006 revision of the Nosology and Classification of Genetic Skeletal Disorders, in which 372 different conditions were placed into 37 groups defined by molecular, biochemical, and/or radiographic criteria (5) (Table 2). The 2006 revision includes even more dysostoses than in the 2002 revision as well as malformation syndromes that have a skeletal component. All these revisions merely reflect the complexity of skeletal-genetic phenotypes. Over the recent years the accumulation of knowledge on genes and proteins responsible for genetic disorders of the skeleton has been unprecedented.

Table 1. Molecular- Pathogenetic Classification of Genetic Disorders of the Skeleton

Gene or protein	Clinical phenotype
Group 1: Defects in extracellular structural proteins	
COLIA1, COLIA2 (collagen 1 αl, α2 chains)	Family: Osteogenesis imperfecta
COL2A1 (collagen 2 αl chain)	Family: achondrogenesis 2,

Gene or protein	Clinical phenotype
	hypochondrogenesis, congenital spondyloepiphyseal dysplasia (SEDC), Kniest, Stickler arthro-ophtalmopathy, familial osteoarthritis, other variants
COL9Al,COL9A2, C01-9A3(collagen 9 α1, α2, α3 chains)	Multiple epiphyseal dysplasia (MED; two or more variants)
COLl0A1 (collagen 10 alchain)	Metaphyseal dysplasia Schmid
COIl IAI, Co111A2 (collagen11 αl, α2 chains)	Oto-spondylo-megaepiphyseal dysplasia (OSMED); Stickler (variant), Marshall syndrome
COMP (cartilage oligoineric matrix protien)	Pseudoachondroplasia, multiple epiphyseal dysplasia (MED, one form)
MATN3 (matrilin-3)	Multiple epiphyseal dysplasia (MED; one variant)
Perlecan	Schwartz jampel type 1; dyssegmental dysplasia
Group 2: Defects in metabolic pathways (including enzymes, ion channels, and transporters)	
TNSALP (tissue nonspecific alkaline phosphatase)	Hypophosphatasia (several forms)
ANKH (pyrophosphate transporter)	Craniometaphyseal dysplasia
TDST/SLC26A2(diastrophic dysplasia sulfate transporter)	Family: achondrogenesis 113, atelosteogenesis 2, diastrophic dysplasia, recessive multiple epiphyseal dysplasia (rMED)
PAPSS2, phosphoadenosine- phosphosulfate-synthase 2	Spondylo-epi-metaphyseal dysplasia Pakistani type
TCIRGI, osteoblast proton pump subunit	Severe infantile osteopetrosis
CIC-7 (chloride channel 7)	Severe osteopetrosis
Carboanhydrase II	Osteopetrosis with intracranial calcifications and renal tubular acidosis
Vitamin K-epoxide reductase complex	Chondrodysplasia punctata with vitamin K-dependent coagulation defects
MGP (matrix Gla protein)	Keutel syndrome (pulmonary stenosis, brachytelephalangism, cartilage calcifications and short stature)
ARSE (arylsulfatase E)	X-linked chondrodysplasia punctata (CDPXI)
3-β-hydroxysteroid-dehydrogenase	CHILD syndrome
3-β-hydroxysteroidΔ(8)Δ(7)- isomerase	X-linked chondrodysplasia punctata, Conradi-Hunermann type (CDPX2); CHILD syndrome
PHEX7 (peroxisomal receptor/importer)	Rhizomelic chondrodysplasia punctata 1
DHAPAT (Di-hydroxy-acetonphosphate-acyltransferase, peroxisomal enzyme)	Rhizomelic chondrodysplasia punctata 2
Alkyl-di-hydroxy-diacetonphosphate synthase	Rhizomelic chondrodysplasia punctata 3

Gene or protein (AGPS; peroxisomal enzyme)	Clinical phenotype
Group 3: Defects in folding and degradation of macromolecules	
Sedlin (endoplasmic reticulum protein with unknown function)	X-linked spondyloepiphyseal dysplasia (SED-XL)
Cathepsin K (lysosomal proteinase)	Pycnodysostosis
Lysosomal acid hydrolases and transporters (sulfatase, glycosidase, translocase, etc.)	Lysosomal storage diseases: inucopolysacchari-doses, oligosaccharidoses, glycoproteinoses (several forms)
Targeting system of lysosomal enzymes (GIcNAc-1-phosphotransferase)	Mucolipidosis (II (I-cell disease), inucolipidosis III
MMP2 (matrix inetalloproteinase 2)	Torg type osteolysis (nodulosis arthropathy and osteolysis syndrome)
Group 4: Defects in hormones and signal transduction mechanisms	
25-α-hydroxycholecalciferol-1-hydroxylase	Vitamin D-dependent rickets type 1 (VDDR1)
1,25-α-dihydroxy-vitamin D3 receptor	Vitamin D-resistant rickets with end-organ unresponsiveness to vitamin D3 (VDDR2)
CASK (calcium “sensor” receptor)	Neonatal severe hyperparathyroidism with bone disease (if affected fetus in unaffected mother) Familial hypocalciuric hypercalcenua
PTH/PTHrP receptor	Metaphyseal dysplasia Jansen Lethal dysplasia Blomstrand
GNAS1 (stimulatory Gsα protein)	Pseudohypoparathyroidism (Albright hereditary osteodystrophy and several variants) with constitutional haploinsufficiency mutations McCune-Albright syndrome with somatic mosaicism for activating mutations
PEX proteinase	Hypophosphatemic rickets, X-linked, semidominant type (impaired cleavage of FGF23)
FGF23, fibroblasts growth factor 23	Hypophosphatemic rickets, autosomal dominant type (resistance to PEX cleavage)
FGFR1 (fibroblast growth factor receptor 1)	Craniosynostosis syndromes (Pfeiffer, other variants)
FGFR2	Craniosynostosis syndromes (Apert, Crouzon, Pfeiffer; several variants)
FGFR3	Thanatophoric dysplasia, achondroplasia, hypochondroplasia, SADDAN Craniosynostosis syndromes (Crouzon with acanthosis nigricans, Muenke nonsyndromic

Gene or protein	Clinical phenotype
	craniosynostosis)
ROR-2 (“orphan receptor tyrosine kinase”)	Robinow syndrome, Brachydactyly type B
TNFRSF1IA (receptor activator of nuclear factor k13; RANK)	Familial expansile osteolysis
TGFRI	Diaphyseal dysplasia (Camurati-Engelmann)
CDMPI (cartilage-derived morphogenetic protein 1)	Acromesomelic dysplasia Grebe/Hunter-Thompson Brachydactyly type C
Noggin (“growth factor,” TGF antagonist)	Multiple synostosis syndrome; synphalangism and hypoacusis syndrome
DLL3 (delta-like 3, intercellular signaling)	Spondylocostal dysostosis (one form)
IHH (Indian hedgehog signal molecule)	Brachydactyly A1
C7orf2 (orphan receptor)	Acheiropodia
SOST (sclerostin; cystine knot secreted protein)	Sclerosteosis, van Buchem disease
LRP5 (LDL receptor-related protein 5)	Osteoporosis-pseudoglioma syndrome
WISP3 (growth regulator/growth factor)	Progressive pseudorheumatoid dysplasia
Group 5: Defects in nuclear proteins and transcription factors	
SOX9 (HMG-type DNA binding protein/transcription factor)	Campomelic dysplasia
6113 (zinc finger gene)	Greig cephalopolysyndactyly, polydactyly type A and others, Pallister-Hall syndrome
TRPS1 (zine-finger gene)	Tricho-rhino-phalangeal syndrome (types 1-3)
EVC (leucine-zipper gene)	Chondroectodermal dysplasia (Ellis-van Creveld)
TWIST (helix-loop-helix transcription factor)	Craniosynostosis Saethre-Chotzen
P63 (p53 related transcription factor)	EEC syndrome, Hay-Wells syndrome, limby-mammary syndrome, split hand-split foot malformation (some forms)
CBFA-1 (core binding factor A1; runt-type transcription factor)	Cleidocranial dysplasia
LXMIB (LIM homeodomain protein)	Nail-patella syndrome
DLX3 (distal-less 3 homeobox gene)	Trichodentoosseous syndrome
HOXD13 (homeobox gene)	Synpolydactyly
MSX2 (horneobox gene)	Craniosynostosis, Boston type Parietal foramina
ALX4 (homeobox gene)	Parietal foramina (cranium bifidurn)
SHOX (short stature-homeobox gene)	Leri-Weill dyschondrosteosis, idiopathic short stature?
TBX3 (T box 3, transcription factor)	Ulnar-mammary syndrome
TBX5 (T box 5, transcription factor)	Holt-Oram syndrome
EIF2AK3 (transcription initiation factor kinase)	Wolcott-Rallison syndrome (neonatal diabetes mellitus and spondyloepiphyseal dysplasia)
NEMO (NFkB essential modulator; kinase	Osteopetrosis, lymphedema, ectodermal

Gene or protein activity)	Clinical phenotype dysplasia and immunodeficiency (OLEDAID)
Group 6:Defects in oncogenes and tumor suppressor genes	
EXTI, EXT2 (exostosin-1, exostosin-2; heparan-sulfate polymerases)	Multiple exostoses syndrome types 1, type 2
SH3BP2 (c-Abl-binding protein)	Cherubism
Group 7: Defects in RNA and DNA processing and metabolism	
RNAse MRP-RNA component	Cartilage -hair-hypoplasia
ADA (adenosine deaminase)	Severe combined immunodeficiency (SCID) with (facultative) metaphyseal changes

Table 2. Nosology and Classification of Genetic Skeletal Disorders (2006)

Groups	Subgroups
1. FGFR3 group	Thanatophoric dysplasia Type I (TD1) Thanatophoric dysplasia Type II (TD2) Severe achondroplasia-developmental delay-acanthosis nigricans (SADDAN) Achondroplasia Hypochondroplasia Hypochondroplasia-like dysplasia
2. Type 2 collagen group	Achondrogenesis type 2 (ACG2; Langer-Saldino) Platyspondylic dysplasia, Torrance type Hypochondrogenesis Spondyloepiphyseal dysplasia congenital (SEDC) Spondylometaphyseal dysplasia (SEMD) Strudwick type Kniest dysplasia Spondyloperipheral dysplasia Mild SED with premature onset arthrosis Stickler syndrome type 1

Groups	Subgroups
	Stickler-like syndrome
3. Type 11 collagen group	Stickler syndrome type 2 Marshall syndrome Otospondylomegaepiphyseal dysplasia (OSMED), recessive type OSMED, dominant type (Weissenbacher-Zweymüller syndrome, Stickler syndrome type 3)
4. Sulphation disorders group	Achondrogenesis type 1B (ACG1B) Atelosteogenesis type 2 (AO2) Diastrophic dysplasia (DTD) MED, autosomal recessive type (rMED; EDM4) SEMD Omani type SEMD Pakistani type
5. Perlecan group	Dyssegmental dysplasia, Silverman-Handmaker type Schwart-Jampel syndrome (myotonic chondrodystrophy)
6. Filamin group	Frontometaphyseal dysplasia Osteodysplasty Melnick-Needles Otopalatodigital syndrome type 2 (OPD1) OPD2 Atelosteogenesis type 1 (AO1)
7. Short-rib dysplasia (SRP) (with or without polydactyly) group	Chondroectodermal dysplasia (Ellis-van Creveld) SRP type 1/3 (Saldino-Noonan/Verma-Naumoff) SRP type 2 (Majewski)

Groups	Subgroups
	SRP type 4 (Beemer) Oral-Facial-Digital syndrome type 4 (Mohr-Majewski) Asphyxiating thoracic dysplasia (ATD; Jeune) Thoracolaryngopelvic dysplasia (Barnes)+
8. Multiple epiphyseal dysplasia and pseudoachondroplasia group	Pseudoachondroplasia (PSACH) Multiple epipyseal dysplasia (MED) type 1 (EDM1) MED type 2 (EDM2) MED type 3 (EDM3) MED type 5 (EDM5) MED type 6 (EDM6) MED, other types Familial hip dysplasia (Beukes) See also EDM4 in Group 4
9. Metaphyseal dysplasias	Metaphyseal dysplasia, Schmid type (MCS) Cartilage-hair-hypoplasia (CHH; metaphyseal dysplasia, McKusick type) Metaphyseal dysplasia, Jansen type Metaphyseal dysplasia with pancreatic insufficiency and cyclic neutropenia (Shwachman-Bodian-Diamond syndrome, SBDS) Metaphyseal anadysplasia Chronic infantile neurologic cutaneous articular syndrome (CINCA)/neonatal onset multisystem inflammatory disease (NOMID) Metaphyseal dysplasia, Spahr type

Groups	Subgroups
	Metaphyseal acroscyphodysplasia
10. Spondylometaphyseal dysplasias (SMD)	Spondylometaphyseal dysplasia, Kozlowski type SMD, Sutcliffe/corner fracture type SMD with severe genuvalgum SMD with cone-rod dystrophy See also disorders in Group 11 as well as SMD Sedaghatian type in Group 12)
11. Spondylo-epi(-meta)physeal dysplasias (SE(M)D)	Dyggve-Melchior-Clausen dysplasia (DMC) Immuno-osseous dysplais (Schimke) Progressive pseudorheumatoid dysplasia (PPRD) SED Kimberley type SED Wolcott-Rallison type SEMD Matrilin type SEMD Missouri type Metatropic dysplasia (various forms) SED tarda, X-linked (SED-XL) Dyssegmental dysplasia, Roland-Desbuquois type SPONASTRIME dysplasia SEMD Maroteaux type (pseudo-Morquio type 2) SEMD short limb-abnormal calcification type SEMD with joint laxity (SEMD-JL) Beighton type SEMD with joint laxity (SEMD-JL) letodactylic

Groups	Subgroups
	or Hall type SEMD Handigodu type Late onset SED, recessive type
12. Severe spondylodysplastic dysplasias	Achondrogenesis type 1A (ACG1A) SMD Sedaghatian type Opsismodysplasia Fibrochondrogenesis Schneckenbecken dysplasia
13. Moderate spondylodysplastic dysplasias (brachyolmias)	Brachyolmia, Hobaek/Toledo types Brachyolmia, autosomal dominant type See also SED-XL and late-onset recessive SED in Group 11
14. Acromelic dysplasias	Trichorbinophalangeal dysplasia,types 1/3 Trichorhinophalangeal dysplasia,type 2 (Langer-Giedion) Acrocapitofemoral dysplasia Angel-shaped phalango-epiphyseal dysplasia (ASPED) Weill-Marchesani sydrome, recessive type Weill-Marchesani sydrome, dominant type Brachydactyly-hypertension syndrome (Bilginturian) Acrodysostosis Acrolaryngeal dysplasia Acromicric dysplasia Cranioectodermal dysplasia (Sensenbrenner)

Groups	Subgroups
	Craniofacial conodysplasia Familial digital arthropathy with brachydactyly Geleophysic dysplasia See also Short rib dysplasias (group 7)
15. Acromesomelic dysplasias	Acromesomelic dysplasia type Maroteaux Grebe dysplasia Fibular hypoplasia and complex brachydactyly (Du Pan) Acromesomelic dysplasia with genital anomalies Acromesomelic dysplasia, Osebold-Remondini type
16. Mesomelic and rhizo-mesomelic dysplasias	Dyschondrosteosis (Leri-Weill) Langer type (homozygous dyschondrosteosis) Robinow syndrome, recessive type Robinow syndrome, dominant type Mesomelic dysplasia, Kantaputra type Mesomelic dysplasia, Nievergelt type Mesomelic dysplasia, Kozlowski-Reardon type Mesomelic dysplasia with acral synostoses (Verloes-David-Pfeiffer type) Mesomelic dysplasia, Savarirayan type (Triangular Tibia-Fibular Aplasia) Omodysplasia, dominant type Omodysplasia, recessive type
17. Bent bones dysplasias	Campomelic dysplasia (CD) Stüve-Wiedemann dysplasia

Groups	Subgroups
18. Slender bone dysplasia group	3M syndrome Kenny-Caffey dysplasia type 1 Kenny-Caffey dysplasia type 2 Microcephalic osteodysplastic primordial dwarfism type 1/3 (MOPD2; Majewski type) Microcephalic osteodysplastic dysplasia, Saul-Wilson type IMAGE syndrome (Intrauterine Growh Retardataion, Metaphyseal Dysplasia, Adrenal Hypoplasia, and Genital Anomalies) Osteocraniostenosis
19. Dysplasias with multiple joint dislocations	Desbuquois dysplasia Recessive Larsen-like syndrome Pseudodiastrophic dysplasia
20. Chondrodysplasia punctata (CDP) group	CDP Conradi-Hünermann type (CDPX2) CDP X-linked recessive, brachytelephalangic type (CDPX1) CHILD (congenital hemidysplasia, icthyosis, limb defects) Greenberg dysplasia Rhizomelic CDP type 1 Rhizomelic CDP type 2 Rhizomelic CDP type 3 Astley-Kendall dysplasia CDP tibial-metacarpal type Dappled diaphyseal dysplasia
21. Neonatal osteosclerotic dysplasias	Blomstrand dysplasia

Groups	Subgroups
	Desmosterolosis Caffey disease (including infantile and attenuated forms) Caffey disesase (severe variants with prenatal onset)Raine dysplasia
22. Increased bone density (without modification of bone shape)	Osteopetrosis, severe neonatal or infantile forms Osteopetrosis, intermediate form Osteopetrosis with renal tubular acidosis Osteopetrosis, late-onset form type 1 Osteopetrosis, late-onset form type 2 Osteopetrosis with ectodermal dysplasia and immune defect (OLEDAID) Pyknodysostosis Osteopoikilosis Melorheostosis with osteopoikilosis Melorheostosis Dysosteosclerosis Osteomesopyknosis Osteopathia striata with cranial sclerosis Osteopetrosis with infantile neuroaxonal dysplasia Osteosclerosis, Stanescu type
23. Increased bone density group with metaphyseal and/or diaphyseal involvement	Craniometaphyseal dysplasia, autosomal dominant type Diaphyseal dysplasia Camurati Engelmann Diaphyseal dysplasia Camurati Engelmann,

Groups	Subgroups
	type 2 Oculodentoosseous dysplasia (ODOD) mild type ODOD severe type Osteoectasia with hyperphosphatasia (Juvenile Paget disease) Sclerosteosis Endosteal hyperostosis, van Buchem type Trichodentoosseous dysplasia Craniometaphyseal dysplasia, autosomal recessive type Diaphyseal medullary stenosis with bone malignancy Craniodiaphyseal dysplasia Craniometaphyseal dysplasia, Wormian bone type Cranio-osteoarthropathy Endosteal sclerosis with cerebellar hypoplasia Lenz-Majewski hyperostotic dysplasia Metaphyseal dysplasia, Braun-Tinschert type Pachydermoperiostosis Pyle disease Deaphyseal dysplasia with anemia (Ghosal
24. Decreased bone density group	Osteogenesis imperfecta type 1 Osteogenesis imperfecta type 2 Osteogenesis imperfecta type 3

Groups	Subgroups
	Osteogenesis imperfecta, recessive, unlinked to COL1A1 and COL1A2 Osteogenesis imperfecta type 4 Osteogenesis imperfecta type 5 Osteogenesis imperfecta type 6 Osteogenesis imperfecta type 7 (so-called “rhizomelic form”) Osteoporosis-pseudoglioma syndrome Bruck syndrome type 1 Bruck syndrome type 2 Singleton-Merten dysplasia Geroderma osteodysplasticum Calvarial doughnut lesions with bone fragility Idiopathic juvenile osteoporosis Cole-Carpenter dysplasia (bone fragility with craniosynostosis) Spondylo-ocular dysplasia Osteopenia with radiolucent lesions of the mandible
25. Defective mineralization group	Hypophosphatasia, perinatal lethal and infantile forms Hypophosphatasia, adult form Hypophosphatemic rickets XLD Hypophosphatemic rickets AD Hypophosphatemic rickets with hypercalciuria Neonatal hyperparathyroidism, severe form

Groups	Subgroups
	Familial hypocalciuric hypercalcemia with transient neonatal hyperparathyroidism Eiken dysplasia
26. Lysosomal storage diseases with skeletal involvement (Dysostosis Multiplex Group)	Mucopolysaccharidosis type 1H/1S Mucopolysaccharidosis type 2 Mucopolysaccharidosis type 3AMucopolysaccharidosis type 3BMucopolysacchmidosis type 3CMucopolysaccharidosis type 3DMucopolysaccharidosis type 4AMucopolysaccharidosis type 4BMucopolysaccharidosis type 6Mucopolysaccharidosis type 7Fucosidosis alpha-Mannosidosis beta- MannosidosisAspartylglucosammuria GM1 Gangliosidosis, several formsSialidosis, several forms Sialic acid storage disease SIASDGalactosialidosis, several forms Multiple sulfatase deficiency Mucolipidosis II Mucolipidosis III
27. Osteolysis group	Familial expansile osteolysis Infantile systemic hyalinosis Mandibuloacral dysplasia type A Progeria, Hutchinson-Gilford type Mandibuloacral dysplasia type B Torg-Winchester syndrome Hadju-Cheney syndrome Multicentric carpal-tarsal osteolysis with and without nephropathy
28. Disorganized development of skeletal components group	Cherubism Fibrous dysplasia, polyostotic form

Groups	Subgroups
	Progressive osseous heteroplasia Gnathodiaphyseal dysplasia Multiple cartilaginous exostoses 1 Multiple cartilaginous exostoses 2 Multiple cartilaginous exostoses 3 Osteoglophonic dysplasia Fibrodysplasia ossificans progressiva (FOP) Carpotarsal osteochondromatosis Cherubism with gingival fibromatosis (Ramon syndrome) Dysplasia epiphysealis hemimelica (Trevor) Enchondromatosis (Ollier) Spondyloenchondrodysplasia (SPENCD) Enchondromatosis with hemangiomata (Maffucci) Genochondromatosis Metachondromatosis Metaphyseal chondromatosis with D-2-hydroxyglutaric aciduria Dysspondyloenchondromatosis Cheiro-spondyloenchondromatosis
29. Cleidocranial dysplasia group	Cleidocranial dysplasia CDAGS syndrome (craniosynostosis, delayed fontanel closure, paretal foramina, imperforate anus, genital anomalies, skin eruption) Yunis-Varon dysplasia

Groups	Subgroups
30. Craniosysnostosis syndromes and other cranial ossification disorders	Pfeiffer syndrome (FGFR1-related) Apert syndrome Craniosynostosis with cutis gyrate (Beare-Stevenson) Crouzon syndrome Pfeiffer syndrome (FGFR2-related) Crouzon-like synostosis with acanthosis nigricans (Crouzonodermoskeletal syndrome) Craniosynostosis Muenke type Antley-Bixler syndrome Craniofrontonasal syndrome Craniosynostosis Boston type Saethre-Chotzen syndrome Shprintzen-Goldberg syndrome Baller-Gerold syndrome Parietal foramina (isolated) Carpenter syndrome
31. Dysostoses with predominant craniofacial involvement	Mandibulo-facial dysostosis (Treacher-Collins, Franceschetti-Klein) Oral-facial-digital syndrome type 1 (OFD1) Weyer acrofacial (acrodental) dysostosis Acrofacial dysostosis, Nager type Frontonasal dysplasia Hemifacial microsomia Miller syndrome (postaxial acrofacial

Groups	Subgroups dysostosis)
32. Dysostoses with predominant vertebral and costal involvement	Currarino syndrome Spondylocostal dysostosis type 1 (SCD1) Spondylocostal dysostosis type 1 (SCD2) Spondylocostal dysostosis type 1 (SCD3) Spondylocostal dysostosis, dominant type Jarcho-Levin syndrome Cerebro-costo-mandibular syndrome (rib gap syndrome) Ischio-spinal dysostosis Klippel-Feil anomaly with laryngeal malformation
33. Patellar dysostoses	Ischiopubic patellar dysplasia Nail-patella syndrome Genitopatellar syndrome Ear-patella-short stature syndrome (Meier-Gorlin)
34. Brachydactylies (with or without extraskeletal manifestations)	Brachydactyly type A1 Brachydactyly type A2 Brachydactyly type A3 Brachydactyly type B Brachydactyly type C Brachydactyly type D Brachydactyly type E Feingold syndrome (microcephaly-oculo-digito-esophageal-duodenal syndrome)

Groups	Subgroups
	Hand-Foot-Genital Keutel syndrome Albright hereditary osteodystrophy (AHO) AHO-like syndrome (Brachydactyly-Mental retardation syndrome) Rubinstein-Taybi syndrome Catel-Manzke syndrome Christian type brachydactyly Coffin-Siris syndrome Mononen type brachydactyly Poland syndrome
35. Limb hypoplasia-reduction defects group	Acheiropodia De Lange Syndrome Fanconi anemia Holt-Oram syndrome Okihiro syndrome (Duane-Radial Ray anomaly) Roberts Syndrome Tetra-amelia Ulnar-mammary syndrome Ankyloblepharon-Ectodermal dysplasia-Cleft lip/palate (AEC) Ectrodactyly-ectodermal dysplasia cleft-palate syndrome type 3 (EEC3) Ectrodactyly-ectodermal dysplasia cleft-palate syndrome type 1 (EEC1)

Groups	Subgroups
	Ectrodactyly-ectodermal dysplasia cleft-palate syndrome type 2 (EEC2) Ectrodactyly-ectodermal dysplasia-macular dystrophy syndrome (EEM) Limb-mammary syndrome (including ADULT syndrome) Split Hand-Foot malformation, isolated form, type 4 (SHFM4) Split Hand-Foot malformation, isolated form, type 1 (SHFM1) Split Hand-Foot malformation, isolated form, type 2 (SHFM2) Split Hand-Foot malformation, isolated form, type 3 (SHFM3) Split Hand-Foot malformation, isolated form, type 5 (SHFM5) Split Hand-Foot malformation with tibial hypoplasia Adams-Oliver syndrome Al-Awadi Raas-Rothschild limb-pelvis hypoplasia-aplasia Femoral hypoplasia-Unusual facies syndrome Femur-Febular-Ulna syndrome Fuhrmann syndrome Hanhart syndrome (Hypoglassia-hypodactylia) Scapulo-iliac dysplasia (Kosenow) Thrombocytopenia-Absent Radius (TAR)
36. Polydactyly-Syndactyly-Triphalangism group	Preaxial Polydactyly type 1 (PPD1)

Groups	Subgroups
	Preaxial Polydactyly type 2 (PPD2)/Triphalangeal Thumb (TPT)
	Preaxial Polydactyly type 3 (PPD3)
	Preaxial Polydactyly type 4 (PPD4)
	Greig Cephalopolysyndactyly syndrome
	Pallister-Hall syndrome
	Fibulin1-associated complex synpolydactyly
	Synpolydactyly
	Syndactyly type 3
	Townes-Brocks syndrome (Renal-Ear-Anal-Radial syndrome)
	Lacrimo-Auriculo-Dento-Digital syndrome (LADD)
	Acrocallosal syndrome
	Acro-pectoral syndrome
	Acro-pectoro-vertebral dysplasia (F-syndrome)
	Mirror-image polydactyly of hands and feet (Laurin-Sandrow syndrome)
	Mirror-image polydactyly of feet with tibial hypoplasia
	Syndactyly type 1
	Postaxial Polydactyly
37. Defects in joint formation and synostoses	Multiple synostoses syndrome type 1
	Multiple synostoses syndrome type 2
	Proximal symphalangism type 1
	Proximal symphalangism type 2

Groups	Subgroups
	Radio-ulnar synostosis with amegakaryocytic thrombocytopenia

Definitions

Osteochondrodysplasias refer to abnormalities of cartilage or bone growth and development. They are divided into i) defects of growth of tubular bones and/or spine which are frequently referred to as chondrodysplasias, e.g., achondroplasia ii) disorganized development of cartilage and fibrous components of the skeleton iii) abnormalities of density or cortical diaphyseal structure and/or metaphyseal modeling (e.g., osteogenesis imperfecta).

Dysostoses refer to malformations of individual bones, single or in combination, and does not refer to a generalized disorder of the skeleton. Many disorders that were previously referred to as dysostoses are now listed with the osteochondrodysplasias, since they are due to mutations of genes associated with dysplasias; e.g. brachydactyly C, Hunter Thompson dysplasia and Grebe dysplasia.

Clinical Evaluation

The clinical evaluation should start with a complete medical history that includes previous growth points. Since skeletal dysplasias may become apparent at various ages, study of growth points since birth may help to narrow the differential diagnosis. The family history should include information about other affected family members and possible consanguinity. Parents should be examined for evidence of disproportionate stature or other evidence of a skeletal dysplasia. Physical examination should focus on anthropometric measurements. The osteochondrodysplasias are generalized disorders of the skeleton, which usually result in disproportionate short stature (Figure 2a and 2b). A disproportionate body habitus may not be readily appreciated unless anthropometric measurements (i.e., arm span, upper to lower segment ratios) are carefully obtained. This assessment may help to determine if the disproportionate shortening affects primarily the trunk or the limbs: the proximal (rhizomelic), middle (mesomelic) or distal segment (acromelic).

The U/L segment ratio can be calculated by measurement of the lower segment from the top of the symphysis pubis to the floor at the inside of the heel. The upper segment is then obtained by subtracting the lower segment from the total height. The U/L ratio can then be calculated and the results compared to published established norms for age and sex. Measurement of arm span provides an assessment of trunk vs limb length. In normal individuals, the arm span is very close to the total height measurement.

Establishing the correct diagnosis

The next step in the evaluation of disproportionate short stature is to obtain a full set of skeletal radiographs including views of the skull, spine, pelvis, extremities, hands and feet. Attention should be paid to the specific parts of the skeleton that are involved, the location of the lesion

within each bone (epiphysis, metaphysis, diaphysis) and the recognition of unique patterns of abnormal skeletal ossification. Review of radiographs taken at different ages or before and after puberty may be helpful, because the radiographic features of many of these disorders may change with age.

Histologic studies of the chondro-osseous tissue may reveal specific abnormalities. Based on histological findings, chondrodysplasias can be grouped into four categories (Table 3).

Table 3. Histologic classification of chondrodysplasias

1. Minimal or no qualitative abnormality in endochondral ossification 1. achondroplasia 2. hypochondroplasia
2. Abnormalities in cellular morphology 1. Large chondrocytes with prominent inclusion 1. achondrogenesis IA 2. pseudoachondroplasia 3. certain SEDs 2. Sparse matrix with collagen rings around the chondrocytes 1. achondrogenesis IB 3. Dilatation of the chondrocyte rough endoplasmic reticulum (RER) 1. SEDs 2. pseudoachondroplasia 3. spondylometaphyseal dysplasia 4. multiple epiphyseal dysplasia (autosomal recessive type) 5. Kniest dysplasia
3. Abnormalities in matrix morphology 1. “Swiss cheese” appearance of cartilage 1. Kniest dysplasia 2. Large lacunae containing numerous chondrocytes 1. Dyggve-Melchior-Clause syndrome 3. Areas of dystrophic ossification, fibrous dysplasia ad fat deposition in the reserve 4. Zone cartilage of the matrix 1. chondrodysplasia punctata 5. Wide interwoven connective septa in epiphyseal cartilage and basal zone 1. fibrochondrogenesis
4. Abnormalities primarily localized to the areas of chondro-osseous transformation 1. Reduced and disorganized columnization 1. thanatophoric dysplasia 2. short rib polydactyly syndrome 2. Broad matrix septa surrounding clusters of hypertrophic cells 1. metaphyseal dysplasias

Management

Effective management requires precise diagnosis, prompt recognition of skeletal and non-skeletal complications, appropriate orthopedic and rehabilitative care, psychosocial support and genetic counseling. Orthopedic management aims at maximizing mobility and correcting deformities. Additional medical therapies have developed in a small number of these disorders.

Given the large number of these disorders, this paper will emphasize those that are clinically more relevant given their frequency, therapeutics or the insights they provide on the pathogenesis of bone disease.

ACHONDROPLASIA GROUP

Achondroplasia

Phenotype: Achondroplasia is due to a defect of endochondral bone formation, which results in rhizomelic shortening of the limbs (Figures 2a and 2b) (6). Final height averages 135cm in men, and 125cm in women. Growth curves for achondroplasia have been developed. The size of the vertebral bodies and the diameter of the posterior vertebral arches are also decreased. Lumbar gibbus is present in infancy, and is replaced later by prominent lumbar lordosis. The mean head circumference follows a curve above the 97% for normal individuals (Figure 5a and 5b). Additional facial features include frontal bossing, hypoplasia of the maxilla, and mandibular prognathism. The foramen magnum is also affected and decreased in size. Therefore, secondary communicating hydrocephalus may develop. Cranio-cervical compression, which may present with upper limb weakness, clonus, apnea or sudden infant death, can be a significant neurologic complication of the small foramen magnum (7-9). Otherwise, life expectancy and mental development is normal. Additional features include recurrent otitis media and serous otitis, which lead to conductive hearing loss.

Hypochondroplasia

Phenotype: Hypochondroplasia has been described as a milder form of achondroplasia, which presents with short stature usually during the second to third year of life (Figure 6). The characteristic facial features of achondroplasia are absent, and both short stature and rhizomelia are less pronounced. Adult height is approximately 120 to 150cm. Common features include genu varum and mild lumbar lordosis (10).

Thanatotropic Dysplasia

Phenotype: This is a lethal type of skeletal dysplasia characterized by extreme shortening of the limbs, large bulging forehead with prominent eyes, small narrow thorax, which may result in respiratory problems, and congenital heart and CNS defects.

Genetics: Achondroplasia is the most common of osteochondrodysplasias, with a frequency of approximately 1:26,000. Although transmitted as an autosomal dominant disorder, 90% of cases represent new mutations. Achondroplasia is caused by mutations of the gene for fibroblast growth factor receptor 3 (FGFR3) located in the short arm of chromosome 4 (11, 12). Patients with thanatotropic dysplasia are homozygotes for the FGFR3 mutations, while patients with achondroplasia or hypochondroplasia are heterozygotes.

Treatment: Treatment is primarily supportive. Primarily care physicians should be alert to the possibility of neurological complications associated with achondroplasia. With regards to treatment of short stature with growth hormone, limited data indicate a modest increase of growth velocity after the first couple of years of growth hormone therapy. However, the concern about worsening of body proportions with this treatment remains.

MESOMELIC DYSPLASIAS

Leri-Weill dyschondrosteosis

Phenotype: This syndrome is characterized by short stature primarily caused by reduction in the middle segments of the distal limbs (mesomelia), and a characteristic abnormality of the forearm, called Madelung deformity (Figure 3). Madelung deformity is the defining feature of Leri-Weill dyschondrosteosis, and consist of shortening and bowing of the radius and distal hypoplasia and dorsal dislocation of the ulna leading to limited mobility of the wrist. The severity of Madelung deformity and other clinical signs vary considerably among patients with Leri-Weill syndrome, with an average height reduction of -2.3 SDS. Adult heights can range from 135cm to normal. Overall, the phenotype is more severe in females and increases in severity with age.(13)

Langer mesomelic dysplasia

Phenotype: This rare disorder is characterized by severe disproportionate short stature with mesomelic shortening of the limbs, hypoplasia of the mandible, ulnar deviation of the hands, distal tapering of the humeri, and hypoplastic fibula, radius and ulna (Figure 4).

Genetics: Both the Leri Weill syndrome and Langer dysplasia are associated with defects of the SHOX gene. The SHOX gene is located in the pseudo-autosomal region on the short arm of the X chromosome. The pseudo-autosomal region is the major area of homology located at the tips of the X and Y chromosomes, and contains genes which escape X inactivation. Two copies of the genes are required for normal activity. The SHOX gene, which encodes a protein that has been shown to act as a transcription factor, is a critical gene involved in growth determination.(14-16) In normal individuals, the SHOX gene is found in two copies. A defect in a single copy of the SHOX gene either by point mutation, deletion or chromosomal rearrangement, which is called haploinsufficiency, results in the short stature of a number of clinical syndromes, including Turner syndrome and Leri Weill dyschondrosteosis.(17) Defects in the SHOX gene have been implicated in the pathogenesis of idiopathic short stature,(18, 19) a heterogeneous group of patients who have short stature for unknown reasons. Current studies

suggest that SHOX mutations occur in approximately 1% of patients with idiopathic short stature. There is now a wealth of evidence that the Leri Weill Syndrome results from SHOX mutations and deletions which occur in a single copy of the gene. Homozygosity of SHOX gene defects, and, therefore, complete absence of any SHOX gene product results in the phenotype of Langer mesomelic dysplasia. In contrast, females with an extra X chromosome (47,XXX) have three copies of the SHOX gene and are taller than the normal 46 XX females. Therefore, it appears that height is directly related to SHOX gene dosage.

DYSPLASIAS WITH DECREASED BONE DENSITY

Osteogenesis imperfecta

Phenotype: Osteogenesis imperfecta is a clinically heterogeneous disorder, which is frequently classified as follows (20): Type IA is characterized by grey- blue sclera, osteoporosis with mild to moderate skeletal fragility, joint laxity, normal dentition and premature hearing loss (Figure 7). Fractures typically commence when the child starts to stand, and increase in frequency after childbirth and with aging, especially after menopause. Type IB includes all the above features found in Type IA, but dentition is also affected. Patients with type II osteogenesis imperfecta manifest severe skeletal fragility, which results in multiple fractures since infancy and may lead to premature death from associated complications and respiratory problems related to thorax deformities. Patients with Type III disease also manifest severe osteoporosis, frequent fractures, progressive bone deformities, and dwarfism secondary to vertebral compression fractures, disruption of the growth plates and bone deformities. Progressive scoliosis and thoracic deformities may result in frequent pneumonias. Sclera is bluish at birth, but becomes progressively white in childhood. Hearing may also be impaired. Type IV has similar disease characteristics as type I, with the main difference being the color of the sclera, which is white in patients of the type IV. A final group, type V, was recently proposed by Glorieux to include patients with osteoporosis, and high frequency of hypertrophic calluses.(21)

Genetics: The mode of inheritance of osteogenesis imperfecta is autosomal dominant, although Type III can be transmitted as both autosomal dominant and autosomal recessive. Approximately 80 to 90% of patients with osteogenesis imperfecta carry mutations in one of the two Type I collagen genes, the COL1A1 or COL1A2 genes (22, 23). The etiologies of the remaining cases, in which no mutations have been identified, remain unclear. Individuals with Type IA osteoporosis imperfecta express only one normal copy of the COL1A1 gene because they have a functionless mutant COL1A1 allele. These individuals synthesize normal collagen but in decreased amounts.(24) Most of the babies with osteogenesis imperfecta Type II have expressed mutations of COL1A1 or COL1A2, which result in the production of abnormal Type I collagen that is being incorporated into the extracellular matrix where it impairs the structure and function of the tissue.(25)

Bone histology: Histomorphometric evaluation of bone biopsies showed decreased cortical width and cancellous bone volume. The degree of cancellous volume reduction may vary among the different types of osteogenesis imperfecta, and is attributed to the increased bone turnover in these patients compared to controls.(26)

Treatment: Until the use of bisphosphonates in osteogenesis imperfecta, orthopedic intervention and support were the mainstays of treatment. Bisphosphonates are potent inhibitors of bone resorption, and are used widely in the treatment of osteoporosis in adults. The pioneer work of Glorieux has shown that the bisphosphonate pamidronate, at the dosage of 7 to 10 mg/kg/year given as an intravenous infusion in cycles every 3 months, resulted in significant improvement of bone density, reduction in the frequency of fractures and relief of chronic bone pain.(27, 28) Linear growth was better in patients treated with pamidronate compared to untreated controls. Intravenous pamidronate has also been used successfully in severely affected neonates.(29) The duration of treatment, the long-term safety, and the use of other bisphosphonates remain important issues for future research.

Growth hormone therapy was studied in patients with osteogenesis imperfecta, because of its anabolic effect on the bone, but did not result in clinically significant improvement in bone density.(30, 31) Transplanted allogenic mesenchymal stromal cells or autografting of genetically modified bone marrow derived mesenchymal stromal cells are being considered and evaluated for the treatment of severe osteogenesis imperfecta.(32, 33)

Idiopathic Juvenile Osteoporosis

Phenotype: This is a rare disease, which mainly affects children between the ages of 8 and 14. It runs an acute phase, which usually lasts 2 to 4 years and almost invariably remits spontaneously. During the acute phase, the child may sustain multiple vertebral compression fractures, and fractures of the long bones, particularly the metaphyses, that lead to back pain, deformity and difficulty in walking.(34) The cause of juvenile idiopathic osteoporosis is unknown, and the diagnosis is based on the exclusion of other causes of secondary osteoporosis (Table 3). Differentiation from mild cases of osteogenesis imperfecta may be difficult. Positive family history, affected dentition and blue sclera indicate osteogenesis imperfecta, however, these features may be absent in mild cases.

Histological studies are limited, and it is unclear if bone resorption or bone formation is primarily affected.(35, 36)

Treatment: Bisphosphonates, calcitriol, calcitonin and fluoride have been tried, but the results are equivocal.(34)

INCREASED BONE DENSITY WITHOUT DISRUPTION OF BONE SHAPE

Osteopetroses

Phenotype: Osteopetroses are rare human genetic disorders characterized by a generalized increase in skeletal mass due to markedly decreased bone resorption (Figure 8). Four types of human osteopetrosis have been defined. The infantile malignant osteopetrosis is a lethal autosomal recessive disease, which leads to anemia, thrombocytopenia and extramedullary

hematopoiesis secondary to crowding of the marrow cavity. A defect in macrophage killing of bacteria frequently leads to severe and overwhelming infection. Optic atrophy and blindness may result from progressive encroachment on the optic

foramina.(37) The autosomal Dominant Type II Osteopetrosis (ADO II) is the most frequent osteopetrosis (5.5/100,000) that presents with increased frequency of fractures.(38) The Autosomal Dominant Type I Osteopetrosis (ADO I) is extremely rare, and is characterized by osteocondensation throughout the skeleton, and thickening of the cranial vault. It is the only form of osteopetrosis that is not associated with increased incidence of fractures.(39) Finally, osteopetrosis with renal tubular acidosis presents with fractures and/or short stature, visual impairment and mental retardation in the first few years of life.

Genetics: Recent studies have shown the defect to be in the osteoclast function and not in osteoclast differentiation.(40) Infantile malignant osteopetrosis is genetically heterogenous, and in some cases is caused by mutations of the TCIRG1 gene. This gene is involved in the function of a vacuolar ATPase present in the lysosomal membranes of osteoclasts, and which is important in the acidification of hydroxyapatite and therefore in its resorption. The genes for autosomal dominant osteopetrosis have not yet been identified. Finally, the osteopetrosis with renal tubular acidosis is due to a defect in the gene encoding carbonic anhydrase type II.

Treatment: Malignant infantile osteopetrosis is lethal unless a successful bone marrow HLA matched donor transplantation is performed.(41) The present data show a 50% survival with a median of 15 months post transplantation. Treatment with interferon gamma has been shown to give some promising results in some patients. Neurosurgical unroofing of the optic foramina may ameliorate the visual disability.

Pyknodysostosis

It is an autosomal recessive osteochondrodysplasia in which patients have short stature, dysmorphic features, osteosclerosis and frequent fractures. As in osteopetrosis there is evidence of decreased bone resorption. These patients have found to have mutations of the cathepsin K gene, which is a lysosomal protein responsible for the proteolytic degradation of the osteoclast.(42)

DISORDERS OF MINERALIZATION

Hypophosphatasia

Phenotype: Hypophosphatasia is an inherited disease characterized by defective bone mineralization, and a deficiency of tissue-non-specific alkaline phosphatase (TNSALP) activity.(43) The disease presents with short stature, bowing of the legs, and is highly variable in clinical expression, ranging from stillbirth without mineralized bone to pathologic fractures which develop only late in adulthood. Depending on the age at diagnosis, five clinical forms are currently recognized: perinatal (lethal), infantile, childhood, adult and odontohypophosphatasia. In some cases, differential diagnosis from osteogenesis imperfecta may be difficult, because of

overlap in clinical and biochemical data. Laboratory findings include decreased serum alkaline phosphatase, elevated serum and urine phosphoethanolamode, radiologic evidence of metaphyseal fraying and decreased bone mass.

Genetics: Hypophosphatemia is due to mutations in the alkaline phosphatase liver type gene, also named the TNSALP gene, localized on chromosome 1p36.1-34.(44) The majority of the mutations are missense mutations, which result in variable residual enzymatic activity, and may explain the great variability of the phenotype. The disease is inherited as an autosomal recessive trait, although in the milder forms of childhood and adult onset both autosomal dominant and recessive inheritance have been described.

Treatment: Genetic counseling and prenatal diagnosis by determination of the TNSALP gene mutations in chorionic villus cells.

Hypophosphatemic rickets

Background – Phosphate homeostasis: Similar to calcium, the serum phosphate level is maintained within a narrow range. The principal organ that regulates phosphate homeostasis is the kidney. Serum inorganic phosphorus is filtered by the glomerulus, and 80% of the filtered load is reabsorbed predominately along the proximal nephron. Regulation of the proximal renal tubular reabsorption is achieved through regulation of the brush border membrane type IIa sodium phosphate co-transporter (NPT2). Parathyroid hormone (PTH) is the best characterized physiological regulator of phosphate reabsorption, but its principal function is to maintain calcium homeostasis. PTH increases urinary phosphate excretion via inhibition of NPT2 expression. In addition, hypophosphatemia stimulates calcitriol synthesis via the 25(OH)D-1a-hydroxylase in the kidney, leading to increased intestinal calcium and phosphate absorption and enhanced mobilization of calcium and phosphorus from bone. The resultant increase in serum calcium concentrations inhibits PTH release, with a subsequent increase in urinary calcium excretion and increase in renal tubular phosphate reabsorption.

Genetics of hypophosphatemic rickets: The study of inherited hypophosphatemic disorders has led to the discovery of new regulators of phosphate homeostasis.(45) X- linked hypophosphatemic rickets is caused by mutations of the PHEX gene (initially called PEX), which is located on chromosome Xp22.1 and encodes a membrane endopeptidase (Zn-metaloprotease), called Phex, mainly expressed in bone and teeth. Recent studies indicate that Phex integrates the phosphate-handling processes, regulating the synthesis and/or degradation of a circulating humoral factor called fibroblast growth factor (FGF)-23.(45-47) Activating mutations of the FGF-23 have been identified in kindreds with autosomal hypophosphatemic rickets, indicating that FGF-23 plays a central role in the pathophysiology of these disorders.(48) Finally, defects of the major renal tubular phosphate transporter, NPT2, have been proposed as the cause of the hereditary hypophosphatemic rickets with hypercalciuria, but no mutations have thus far been identified in affected kindreds.(49)

X-linked hypophosphatemic rickets

Phenotype: X-linked hypophosphatemic rickets accounts for 80% of cases of familial phosphate wasting, and is, therefore, the most common inherited hypophosphatemic disorder. Clinically, X-linked hypophosphatemic rickets may present at around 6 months with frontal bossing and mild bowing of the lower limbs. Impaired growth and progressive worsening of the leg bowing may be observed by 12 months, as the infant begins to walk. In the absence of treatment, affected children show poor statural growth and progressive deformity of the legs, leading to abnormal gait. Dentition may be late, and poor dental development may be associated with spontaneous dental abscesses. In adults, the lower limb deformities cause arthralgias and arthritis. Ectopic calcification of the spinal ligaments and the Achilles tendon is a common late complication. Muscle weakness, a major feature of vitamin D deficiency and phospate deprivation, is strikingly absent. Phenotype is frequently more severe in affected males compared to females, in whom the findings of the disease may be much more variable and limited only to low serum phosphate levels.

Biochemical findings: Hypophosphatemia occurs as a result of decreased renal tubular phosphate reabsorption. Serum calcitriol levels are reduced or inappropriately normal for the degree of hypophosphatemia, while calcium and PTH levels are normal. Aberrant regulation of 25(OH)D-1-?-hydroxylase accounts for the low or inappropriately normal levels of calcitriol in the face of hypophosphatemia.

Management: Oral supplementation with phosphate combined with vitamin D is effective in correcting hypophosphatemia, improving growth and reducing leg deformities.(50-52) Phosphate therapy must be given in five divided doses, while the most effective vitamin D replacement is calcitriol. Close monitoring of biochemical parameters is necessary to avoid hypercalcemia and hypercalciuria. Nephrocalcinosis is therefore a common complication of treatment, and renal ultrasounds are recommended on an annual basis. Renal impairment, however, is rare. Growth hormone treatment has been shown to increase final height in patients with X-linked hypophosphatemic rickets; however, truncal growth increased to a much greater extent than leg growth, resulting in an exaggeration of disproportionate truncal height.(53) Finally, orthopedic care and surgical correction of limb deformities, especially during puberty, are part of an effective treatment plan.

Autosomal hypophosphatemic rickets

Phenotype: This disorder is characterized by low serum phosphorous concentrations and phosphaturia, due to impaired renal tubular renal reabsorption of phosphorus, associated with inappropriately low or normal 1, 25 (OH)2D levels. These biochemical abnormalities result in rickets and osteomalacia. The childhood onset is phenotypically similar to X-linked hypophosphatemic rickets. The adult form presents with osteomalacia and bone pain, fractures, muscle weakness, but no bone deformities.(54)

Hereditary hypophosphatemic rickets with hypercalciuria

Phenotype. Patients with this disorder present with osteomalacia, bone pain, rickets, muscle weakness and growth retardation.(55) The biochemical characteristics of the syndrome are

hypophosphatemia and phosphaturia secondary to decrease renal reabsorption of phosphate, and elevated levels of calcitriol, which account for the hypercalciuria. PTH levels are not elevated, suggesting that the increased calcitriol concentrations represent a normal response to hypophosphatemia.

The vitamin D system

Background – the metabolism and action of vitamin D: Vitamin D is formed in the skin by photocatalysis. The vitamin D (cholecalciferol) pathway includes an initial hydroxylation in the liver by the 25-hydroxylase and further 1?-hydroxylation to calcitriol in the renal mitochondria under tight PTH regulation. Vitamin D metabolites, ans primarily calcitriol, lead to calcium absorption by the gut and have direct biologic effects on osteocytes.

Vitamin D dependent rickets type I (deficiency of the 1?-hydroxylase)

Phenotype: Clinical symptoms are similar to vitamin D deficiency, which progressively worsen if diagnosis and treatment are delayed. Symptoms are those of rickets, and include failure to thrive, hypotonia, deformities of the spine and long bones (bowing of legs), as well as generalized muscle weakness and growth retardation. Additional features include a wide frontal fontanelle, frontal bossing, craniotabes, enamel hypoplasia, rachitic rosary and widening of metaphyseal areas as evidenced by enlargement of wrists and ankles.

Diagnosis: Hypocalcemia may occur before any radiological findings of rickets and may result in convulsions. Hypocalcemia leads to secondary hyperparathyroidism and hypophosphatemia.

Genetics: Vitamin D dependent rickets type I is caused by deficiency of the 1a-hydroxylase gene. It is transmitted as an autosomal recessive disorder.(56, 57)

Management: The treatment of choice is life long replacement with 1,25 (OH)2D3, initially at the dosage of 1 to 2 µg daily, followed by a maintenance dose of 0.5 to 1 ug daily. Such treatment corrects biochemical abnormalities and results in rapid and complete resolution of clinical symptoms. Adequate calcium supplementation during the initial bone-healing phase is important. Regular monitoring of calcium excretion to avoid hypercalciuria and calcium deposition in the kidney is recommended.

Hereditary vitamin D resistant rickets

Phenotype: Clinical manifestation is similar to rickets.(58) In addition, many patients have partial or complete alopecia.

Genetics: In the majority of cases, the disease is caused by mutations in the vitamin D receptor.

Treatment: The disease is resistant to even high doses of vitamin D but is responsive to intravenous or oral calcium.

DISORDERS OF PARATHYROID HORMONE ACTION

Jansen's metaphyseal chondrodysplasia

Phenotype: This is a rare form of short limb dwarfism secondary to severe growth plate abnormalities. Dysmorphic features at birth may be variable, and include micrognathia, hypertelorism, high skull vault, wide cranial sutures and high arched palate. Choanal atresia and/or rib fractures may result in postpartum respiratory distress. Severe disproportionate short stature with bowing of the legs, waddling gait and short lower extremities compared to the relative long arms become more obvious as the child grows.

Diagnosis: Biochemical findings are similar to hyperparathyroidism, with asymptomatic hypercalcemia and hypophosphatemia, which persist throughout life, and low or undetectable concentrations of PTH and PTHrP.(59) Radiographic findings change throughout life. In infancy, findings include marked rickets-like metaphyseal changes and radiographic findings as seen in hyperparathyroidism (i.e. loss of normal cortical outline, subperiosteal bone resorption and generalized osteopenia). Rachetiform deformities gradually disappear and irregular patches of partially calcified cartilage start protruding into the diaphyses during childhood, which gradually disappear during adolescence, giving way to a more normal trabecular pattern during adulthood. However, the ends of the tubular bones remain enlarged and expanded.(60, 61)

Genetics: Activating mutations of the receptor of PTH/PTHrP are shown to cause Jansen's metaphyseal chondrodysplasia.(62) Identification of the molecular defect of this rare disorder provides important new insight on the role of PTH/PTHrP receptor on skeletal development. It appears that both PTH and PTHrP stimulate the proliferation of chondrocytes in growth plates, inhibit the differentiation of these cells into hypertrophic chondrocytes and inhibit mineralization. Inheritance of Jansen's dyplasia is autosomal dominant, generally without a positive family history suggestive of spontaneous mutation.

Pseudohypoparathyroidism (PHP)

Phenotype: The term describes a group of conditions in which there is a variable degree of resistance to PTH and a characteristic clinical phenotype of disproportionate short stature, with selective distal shortening of tubular bones, predominantly of metacarpals but also of metatarsals and phalanges, round face, and obesity. The best characterized form of the disorder is known as PHP Type Ia, and includes the combinations of the above described clinical features with complete resistance to PTH. In addition there is high frequency of mental retardation (mean IQ in the range of 60) and ectopic subcutaneous or intracranial calcifications.(63) In many instances there is tissue resistance to the effects of other biological hormones, e.g., thyroid hormone or gonadotropins. Growth hormone (GH) deficiency has been reported to be present in 69% of patients with PHP Type Ia and may represent resistance to GH releasing hormone.(64, 65) Type Ib refers to the presence of PTH resistance without skeletal features. Finally, in pseudo-pseudohypoparathyroidism, the somatic features of pseudohypoparathyroidism occur in the present of normal serum chemistries and normal response to PTH.

Diagnosis: Biochemical findings include hypocalcemia, which may result in seizures or tetanic episodes, and hyperphosphatemia in the face of elevated serum PTH concentrations.

Genetics: The PTH receptor belongs to the G-protein-coupled family receptors. Pseudohypoparathyroidism Ia is caused by a defect in the α subunit of the stimulatory G-protein (GNAS1). GNAS1 is imprinted in a tissue-specific manner in humans, and renal expression of GNAS1 appears to be determined by the maternal allele. Family studies indicate that maternal transmission of the mutation in GNAS1 results in pseudohypoparathyroidism (PHP) Ia.(66) Growth hormone deficiency has been reported to be commone (69% of patients with PHP Ia) Pseudopseudohypoparathyroidism is caused by paternal transmission of a mutated GNAS1 gene; in such cases, the normal maternal allele results in normal renal responsiveness to PTH. To date, no mutations in the GNAS1 have been identified in the patients with pseudohypoparathyroidism Ib. Finally, a variant of pseudohypoparathyroidism Ia associated with precocious male puberty has been attributed to a temperature-sensitive Gsa protein. This unstable protein functions poorly at body temperature in most tissues, but is stable at 32oC, and therefore, permits testicular function.(67)

Management: The aim of treatment is to normalize serum calcium levels with calcium (50-100 mg/kg day of elemental calcium) and vitamin D supplementation. Calcitriol is the vitamin D replacement of choice. Serum calcium levels are maintained at the low normal range.

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