BONE DYSPLASIA SOCIETY
First Meeting

Bigler Auditorium
The Children's Memorial Hospital
Fullerton and Lincoln
Chicago, Illinois

June 17 - 19, 1993
PROGRAM
of the
First Meeting

THE BONE DYSPLASIA SOCIETY

Chicago, Illinois
June 17 - 19, 1993
BONE DYSPLASIA SOCIETY MEETING IS SUPPORTED IN PART BY

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Abstracts of the Founding Members Presentations ........... 6-17-93 9:15 am

Abstracts of the Presentations .............................. 6-18-93 8:20 am

Abstracts of Unknown Case Presentations .................. 6-19-93 10:15 am

Other Case Presentations .................................. 6-19-93 3:05 pm

Poznanski's Personal Selections .............................

A Restaurant Guide .......................................... End
WELCOME

Welcome to beautiful Chicago, site of the 1993 Bone Dysplasia Society Meeting. On behalf of the Society I welcome you all, members and guests, to this eventful meeting.

The Society and I have been working all year to organize a special opportunity for continuing education and scientific presentations.

While you are here, we hope that you will take some time to explore the city. The hotels for the meeting are on the Michigan Avenue - "The Magnificent Mile." Within close walking distance is the best collection of shops anywhere in the United States. The hotels are also close to several interesting museums and many art galleries. There are many wonderful restaurants within close walking distance. If you are interested in architecture, the Architectural Society offers a wonderful tour by boat. They have an excellent walking tour as well.

The lakefront is only a few blocks away. You can sun yourself on a sandy beach or even swim although the water may be cold in June. Jogging along the lake or in the adjacent parks is a popular pastime.

I hope that you enjoy your stay here in Chicago.

Andrew K. Poznanski, M.D.
HISTORY OF THE BONE DYSPLASIA SOCIETY

At the meeting of the international working group on bone dysplasias in Bad Honnef, Germany in 1991, the group decided that it would be worthwhile to form a new society dealing with bone dysplasias and related congenital malformation syndromes which would be open to all physicians, geneticists and other scientists so as to stimulate interest and help advance our understanding of these disorders.

The new nomenclature classification published by the founding group in the European Journal of Pediatrics 151:407-415, 1992 has added considerable new information since the previous classification. It includes chromosomal location, gene locus, protein involved as well as inheritance.

We are currently in an exciting era in our understanding of the bone dysplasias. To further our knowledge we need input from basic scientists, geneticists, radiologists, orthopedic surgeons as well as other medical specialists. Hopefully this Bone Dysplasia Society can provide a forum where ideas can be exchanged and therefore our knowledge of these disorders advanced.
FOUNDING MEMBERS

Peter Beighton
Andres Giedion
Robert J. Gorlin
Judith G. Hall
William A. Horton
Kazimierz S. Kozlowski
Ralph S. Lachman
Leonard O. Langer, Jr.
Pierre Maroteaux
Andrew K. Poznanski
David L. Rimoni
David O. Sillence
GENERAL INFORMATION

SLIDE READY ROOM
- Radiology Library - follow sign and/or map
- Hours: 6-17-93 7:30 am - 5:25 pm
  6-18-93  7:10 am - 5:05 pm
     6-19-93  7:30 am - 4:00 pm
- Double projection will be provided in Bigler Auditorium. Can preview slides in double projection.
- Facility for projection of x-rays will be available, in addition to double projection for slides, on Saturday, June 19.

LUNCHES
- Will be served in the Nellie A. Black Building (NAB) gym which is across the Fullerton Street from Bigler Auditorium.
- NO HIGH HEEL SHOES are allowed on the gym floor as they may damage the floor.

MESSAGES
- Please have messages left at (312) 880-3520.
- These will be posted near/in Bigler Auditorium.

HOTELS
- Westin, 909 N. Michigan Ave., (312) 943-7200
- Allerton, 701 N. Michigan Ave., (312) 440-1500

TRANSPORTATION
- Bus service is available to and from the Westin and Allerton Hotels.
- At other time, taxis are readily available.
- The number 11 bus stop is on Lincoln Avenue near Children’s. This bus goes to Michigan Avenue.

SUPPORT STAFF
- Sally Gartman
- Aidee Guerrero
- Teresa Hedro
- Adrianne Smith
SUMMARY OF ACTIVITIES

Thursday, June 17, 1993

7:30 a.m.   Buses leave from Allerton & Westin Hotels
8:00 a.m. - 9:00 a.m.   Registration - Bigler Auditorium
9:00 a.m. - 9:15 a.m.   Opening Remarks
9:15 a.m. - 10:30 a.m.   Founding Members Presentations
10:30 a.m. - 10:50 a.m.   Coffee Break
10:50 a.m. - 12:30 p.m.   Founding Members Presentations
12:05 p.m. - 1:20 p.m.   Lunch Break - NAB gym
1:20 p.m. - 3:00 p.m.   Founding Members Presentations
3:00 p.m. - 3:20 p.m.   Afternoon Break
3:20 p.m. - 5:08 p.m.   Founding Members Presentations
5:30 p.m.   Buses leave for Allerton & Westin Hotels

Friday, June 18, 1993

7:30 a.m.   Buses leave from Allerton & Westin Hotels
8:10 a.m. - 8:20 a.m.   Introduction - Bigler Auditorium
8:20 a.m. - 10:12 a.m.   Presentations
10:12 a.m. - 10:30 a.m.   Coffee Break
10:30 a.m. - 11:54 p.m.   Presentations
11:54 p.m. - 1:16 p.m.   Lunch Break - NAB gym
1:16 p.m. - 3:08 p.m.   Presentations
3:08 p.m. - 3:25 p.m.   Afternoon Break
3:25 p.m. - 4:49 p.m.   Presentations
5:10 p.m.   Buses leave for Allerton & Westin Hotels
7:00 p.m. - 7:45   Cocktails - Dr. M. Tachdjians, 175 E. Delaware
                   See insert.
8:00 p.m. - until   Welcome to Chicago Dinner - Spiaggia Restaurant
                   Private Dining Room, 980 N. Michigan Avenue

Saturday, June 19, 1993

8:00 a.m.   Buses leave from Allerton & Westin Hotels
8:30 a.m. - 8:40 a.m.   Introduction - Bigler Auditorium
8:40 a.m. - 9:55 a.m.   Presentations
9:55 a.m. - 10:10 a.m.   Coffee Break
10:10 a.m. - 12:20 p.m.   Presentations
12:20 p.m. - 1:30 p.m.   Lunch Break - NAB gym
1:30 p.m. - 3:05 p.m.   Unknown Case Presentations
3:05 p.m. - 3:45 p.m.   Other Case Presentations
4:05 p.m.   Buses leave for Allerton & Westin Hotels
BONE DYSPLASIA SOCIETY MEETING - Thursday, June 17, 1993
FOUNDING MEMBER PRESENTATIONS

8:00  Registration

9:00  Opening Remarks, Andrew K. Poznanski, M.D.
Moderator: Judith Hall, M.D.

9:15  Andres Giedion, M.D.
"The Impact of the 4th Dimension for the Understanding of Radiological Findings in Genetic Bone Disease"

9:40  Ralph S. Lachman, M.D.
"Fetal Imaging in the Skeletal Dysplasia (Overview and Experience)"

10:05 Peter Beighton, M.D.
"Familial Hip Joint Dysplasias - Biomolecular Abnormalities"

10:30  BREAK
Moderator: Peter Beighton, M.D.

10:50 Judith G. Hall, M.D.
"Non-Traditional Types of Inheritance as they Relate to Skeletal Dysplasias"

11:15 David L. Rimoin, M.D.
"Clinical-Molecular Correlations in the Skeletal Dysplasias"

11:40 William A. Horton, M.D.
"Extending the Nosology of the Chondrodysplasias to the Cellular and Molecular Levels"

12:05  LUNCH

Moderator: Robert Gorlin, D.D.S.

1:20  David Silience, M.D.
"Craniocervical Anomalies in Osteogenesis Imperfecta Genetic and Molecular Correlation"

1:45  Jurgen W. Spranger, M.D.
"The Kniest-Stickler Family of Bone Dysplasias"

2:10  Kazimierz S. Kozlowski, M.D.
"Spondylometaphyseal Dysplasia"

2:35  Leonard O. Langer, Jr., M.D.
"Mesomelic and Acromesomelic Bone Dysplasias"
3:00 BREAK

Moderator: David Silince, M.D.

3:20 Robert J. Gorlin, D.D.S.
"Craniotubular Dysplasias"

3:45 Pierre Maroteaux, M.D., M. Le Merre
"Fibrous Dysplasia and Myxomas"

4:10 Andrew K. Poznanski, M.D.
"Punctate Epiphyses: A Radiologic Sign Not a Disease"

4:40 R.J. Gorlin, L.O. Langer, Jr., D. Donnai
"Spondylolocapitosarsal Fusion Syndrome - A New Autosomal Recessive Condition"

4:54 R. Ogle, K. Kozlowski, D. Silince
"A New Syndrome of Delayed Osseous Maturation, Short Stature and Cardiac Anomalies"

5:08 CLOSE OF MEETING FOR THURSDAY
BONE DYSPLASIA SOCIETY MEETING – Friday, June 18, 1993
PRESENTATIONS

8:10 Introduction

Moderator: David Rimoin, M.D.

8:20 C.M. Hall, D.G. Shaw
"A Distinct Form of Spondyloepimetaphyseal Dysplasia with Dislocations"

8:34 M. Vikkula, R. Ritvaniemi, A.F. Vucrio, I. Kaitila, L. Ala-Kokko, L. Peltonen
"Spondyloepimetaphyseal Dysplasia Caused by a Gly → Arg Mutation in Type II Collagen"

8:48 H. Stoess, J. Spranger, B. Pontz
"Comparative Morphological Investigations on the SED-Congenita Family"

9:02 J. Bonaventure, P. Ritvaniemi, P. Freisinger, D. Leguellec, S. Franc, L. Ala-Kokko, P. Maroteaux
"Glycine to Alanine Substitution in the Type II Collagen of a Patient with Hypochondrogenesis"

9:16 C.M. Hall, D.G. Shaw
"Clinical and Radiological Features of Skeletal Dysplasias Localizing to the Long Arm of Chromosome 12"

9:30 A. Nerlich, I. Wisel, T. Schramm
"Immunolocalization of Interstitial Collagen Types in Bone and Cartilage from Two Patients with Severe, Lethal Achondrogenesis Type I"

9:44 I. Kaitila, O. Makitie, T. Sulisalo
"Phenotypic Expression of CHH Gene Responsible for Cartilage-Hair Hypoplasia"

9:58 M. Irms, R.G.K. McCauley
"A Patient with Unusually Severe Radiographic and Physical Manifestations of Cleidocranial Dysostosis"

10:12 BREAK

Moderator: Andres Giedion, M.D.

10:30 G. Nishimura, K. Kozlowski
"A New Sclerosing Bone Dysplasia Mimicking Dysosteosiscrosis"

10:44 B.B. Gay, Jr., L.J. Elsas, J.B. Wyly
"Osteopathia Striata with Cranial Sclerosis"
10:58  B.D. Hall, C.C. Mabry
"Familial Hypocalciuric Hypercalcemia Mimicking Skeletal Dysplasia"

11:12  M. Irons
"Restrictive Lung Disease and Oral Dyspraxia in Kniest Dysplasia"

11:26  M. Robinow, A. Veghte, J. Sonek
"The Femoral Hypoplasia - Unusual Facies Syndrome in 4 Generations"

"Bowing of the Legs with Metaphyseal Involvement: An Emphasis on Differential Diagnosis and a Special Consideration to Schmid Type Metaphyseal Chondrodysplasia (SMCD)"

11:54  LUNCH

Moderator: Jurgen Spranger, M.D.

1:16  Z. Gucev, O. Lekovska, V. Tasic, G. Zafirovski
"Five Members in Three Family Generations with Metaphyseal Dysostosis Schmidt"

1:30  F.A. Beemer, M.G.E.M. Ausems
"A Possible Case of Desbuquois Syndrome: Homogeneity or Heterogeneity?"

1:44  M. Ramsing, Y. Mehraein, M. Espeel, R.B.H. Schutgens, H. Rehder
"Heterogeneity in Chondrodysplasia Punctata"

1:58  T. Costa, G. Tiller, D. Chitayat, E. Silverman
"Maternal Systemic Lupus Erythematosus (SLE) and Chondrodysplasia Punctata in Two Infants. Coincidence or Association?"

2:12  G.F. Eich, T. Costa, A. Giedion
"The 'Elephant's Leg Dysplasia': A New Mesomelic and Acromelic Short Limbed Dwarfism"

2:26  H. Chen, S. Yang
"A De Novo 17q Paracentric Inversion Mosaicism in a Patient with Beemer-Langer Type Short Rib-Polydactyly Syndrome"
Friday, June 18, 1993
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2:40 W. Wertelecki, J.E. Martinez, W.R. Blackburn, H. Chen
"Atelosteogenesis - Boomerang Dysplasia (ATG-BD) and
CNS Abnormalities"

2:54 H. Takano, T. Aihara, G. Nishimura
"Neonatal Radiological Changes of Frontometaphyseal
Dysplasia (FMD)"

3:08 BREAK

Moderator: William A. Horton, M.D.

3:25 E. Latta, M. Ramsing, J. Spranger
"Microcephalic Osteodysplastic Primordial Dwarfism Type
II (MOPD II) in a Boy with Consanguineous Parents"

3:39 M.L. Warman, M. Abbott, S.S. Apte, T. Hefferon,
I. McIntosh, D.H. Cohn, J.T. Hecht, B.R. Olsen,
C.A. Francomano
"Schmid Metaphyseal Chondrodysplasia is Caused by a
Mutation in the Gene for Type X Collagen"

3:53 J.H. Hersh, M.R. Joyce, J. Spranger
"A New Skeletal Dysplasia and Associated Multiple Organ
System Abnormalities"

4:07 L.W. Young, G.A. Rouse, C. Zuppan, C. Sandlin
"Presumed Autosomal Dominant Fetal Akinesia Sequence:
Findings in Sibs and Half Sibs from the Same Mother"

4:21 D. Kumar, J.P. Masel
"A New Syndrome of Mullerian Dysgenesis, Facial
Hypoplasia, Bilateral Forearm Deformity, Brachydactyly,
Spinal Stenosis and Scoliosis"

4:35 E. Nii, K. Obokata, H. Yada, Y. Ogihara, M. Yamazaki,
T. Oki
"Two Siblings with Galactosialidosis"

4:49 CLOSE OF THE SCIENTIFIC SESSION FOR FRIDAY

7:00 Cocktails at Dr. Mihran Tachdjian's. Beautiful view
from the 89th floor of the Hancock Building, enter at
175 E. Delaware. See insert for details.

8:00 Welcome to Chicago Dinner at Spiaggia
980 N. Michigan, (312) 280-2750
BONE DYSPLASIA SOCIETY MEETING - Saturday, June 19, 1993
PRESENTATIONS

8:30  INTRODUCTION: Andrew K. Poznanski, M.D.
Moderator: Andres Giedion, M.D.

8:40  M.L. Kulkarni, S. Koshy, C. Sureshkumar
"A Clinical and Radiological Study of Skeletal
Dysplasias"

8:55  M.H. Hast, D.H. Garrison, A.K. Poznanski
"Was Vesalius a Dwarf?"

9:10  P. Beighton, E. Sujansky, B. Patzak, K.A. Portelet
"Deformed Dwarfs of Vienna"

9:25  A.K. Poznanski, J. Buikstra, S. Burgess
"Ancient Skeletons of an Achondroplastic Mother and
Infant"

9:40  C.B. Graham
"Less Well Known Aspects of Classic Osteopetrosis"

9:55  BREAK

10:10 UNKNOW CASE PRESENTATIONS
Panel Members: J. Spranger, R.S. Lachman

10:15  V. Harris, S. Young, A. Wilks, K. Harris
"Unknown Dwarf"

10:30  F.A. Beemer, P.P.G. Kramer
"Severe Mesomelic Dwarfism, Bifid Spine and Cleft
Palate"

10:45  L.M. Drummond-Borg
"Unknown Case"

11:00  D.S. Newcombe, A.K. Poznanski
"Unknown Case"

11:15  UNKNOW CASE PRESENTATIONS
Panel Members: L.O. Langer, D. Silence

11:20  B. Pontz, P. Freisinger, A. Nerlich, H. Stoess, D.
Färber, F. Maroteaux
"A New Type of a Severe Micromelic
Osteochondrodysplasia (OCD) with Platyspondyly and
Large Metaphyses"

11:35  H. Stoess, B. Kühn, J. Spranger
"Unusual Lethal Bone Dysplasia with Bowed Legs"
Saturday, June 19, 1993

11:50  J.J. Hoo, M.B. Sheinkop
       "A New Spondyloepiphyseal Dysplasia Syndrome?"

12:05  P.S. Karnes
       "Unknown Case"

12:20  LUNCH

1:30   UNKNOWN CASE PRESENTATIONS
       Moderator: Andrew K. Poznanski, M.D.
       Panel Members: All Founding Members

1:35   P. Beighton
       "Unknown Case #1" or "Unknown Case #2"

1:50   R.S. Lachman, D. Rimoin
       "Unknown Case #1"

2:05   P. Beighton, P. Zack
       "Unknown Case"

2:20   M. Le Merrer, P. Maroteaux
       "Unknown Syndrome"

2:35   R.S. Lachman, D. Rimoin
       "Unknown Case #2"

2:50   H. Taybi
       "Unknown Case"

3:05   OTHER CASE PRESENTATIONS

3:45   END OF 1993 BONE DYSPLASIA SOCIETY MEETING
FOUNDING MEMBERS
PRESENTATIONS
June 17, 1993
Confronted with radiological documents of genetic bone disease the observer is often frustrated by the seemingly unspecific or minimal findings in conditions with an apparently typical, well described ikonography. To make it worse, the invisible landmark is often included in the name of the condition.

One easily forgets, that characteristic shapes, pattern etc., compared with a normal lifespan, may be present only during a very limited period of time. To understand and diagnose a certain bone dysplasia for example, among other aspects, we have to learn its natural history, and, speaking of the fourth dimension, its evolution during the lifetime of a patient.

When does a certain finding become detectable the first time? Prenatally, and in which week of pregnancy? A most important consideration for prenatal diagnosis and genetic counselling! At birth, during infancy, childhood or adolescence? And from what period later on will we look in vain for a classical sign, because it may already have been obliterated by skeletal maturation or unspecific secondary changes?

Finally, certain findings can be understood as reminders of ontogenetical or phylogenetical ancient shapes and structures, thus extending the fourth dimension even beyond that of mankind.

The concept is illustrated by various mostly personal longitudinal observations of bone dysplasias and other genetic bone diseases.
FETAL IMAGING IN THE SKELETAL DYSPLASIA (OVERVIEW AND EXPERIENCE). Ralph S. Lachman, M.D., Reuven Sharony, M.D., and Valerie Rappaport, M.D.
Medical Genetics and the International Skeletal Dysplasia Registry, Cedars-Sinai Medical Center, UCLA School of Medicine, Los Angeles, CA.

The skeletal dysplasias (osteochondrodysplasias) comprise a heterogeneous group of disorders that are characterized by generalized abnormalities of skeletal growth and development. Of the approximately 125 well described skeletal dysplasias about 50 are clinically apparent and identifiable at birth. The prevalence of these dysplasias in the newborn is quite frequent and has been estimated to be between 3-4.5 per 10,000, and the overall frequency of skeletal dysplasias among perinatal deaths to be about 9 per 1,000. Over the past 23 years we have acquired an enormous experience in the International Skeletal Dysplasia Registry with skeletal dysplasias diagnosable at birth or earlier. More and more cases referred to the registry over the past 15 years have been diagnosed as abnormal by ultrasound during the second trimester.

I shall present to you the results of our evaluation of over 200 fetuses and stillbirths which had detailed prenatal history and post mortem evaluation including radiographs, chondro-osseous morphology and even some biochemical and molecular studies. As a result of these findings I shall go on to describe the present "state of the art" of fetal imaging as relates to the field of skeletal dysplasias; including screening ultrasound, skeletal dysplasia specific ultrasound, intrauterine fetography (radiography), post mortem radiography and other (ancillary) studies. The use of this created algorithm in the future should result in correct and earlier diagnoses, more informed decision making for pregnancy outcome, and better genetic counseling for future pregnancies as well.
FAMILIAL HIP JOINT DYSPLASIAS - BIMOLECULAR ABNORMALITIES

P. Beighton, R. Ramesar, D. Viljoen (Medical School, University of Cape Town, Observatory 7925, South Africa)

A number of autosomal dominant skeletal dysplasias are characterized by predominant premature osteoarthritis of the hip joint, with lesser changes in the spine and other regions of the skeleton. These conditions are of considerable practical importance, as surgical replacement of the hip joint is often necessary.

As type II collagen is a major component of cartilage, the determinant gene (COL2A1) has been used as a candidate locus in linkage investigations in these families.

The following results have been obtained:

- Namaqualand hip dysplasia (45 persons in 5 generations), linked, LOD 7.98;
- Spondyloepiphyseal dysplasia type Cape Town (13 affected persons in 3 generations), linked, LOD 4.51;
- Beukes hip dysplasia (47 affected persons in 8 generations), unlinked;
- Spondyloepiphyseal dysplasia type Kimberley (11 affected persons in 4 generations), unlinked.

Mseleni joint disease, a severe generalized osteoarthropathy which affects several hundred persons in North Zululand, has also been studied. Preliminary molecular investigations indicate the gene for COL2A1 is not implicated in this disorder.
NON-TRADITIONAL TYPES OF INHERITANCE AS THEY RELATE TO SKELETAL DYSPLASIAS

J. Hall (The University of British Columbia, Vancouver, B.C., Canada)

In the last few years, there have been a number of new mechanisms defined which can lead to genetic disease. These mechanisms turn out to be quite relevant to the skeletal dysplasias.

Mosaicism is the presence of at least two cell lines differing in genotype or karyotype, in a single individual or tissue, which have been derived from a single zygote. There are many bony conditions that are patchy, Olliers', McCune Albright, multiple exostosis, etc., which may be best explained on the basis of mosaicism. Recent developments have shown that McCune Albright syndrome involves mutations of the alpha subgroup of the G\textsubscript{\texti{i}} protein in a patchy mosaic pattern. This was predicted by the tissue types involved in McCune Albright syndrome. It can be anticipated that other conditions with patchy distribution will have alterations in the genotype or karyotype of those cells. Mosaicism can present because of changes in single genes, chromosomes, inactivation, imprinting, etc. It would appear that in multiple exostosis, there may be a '3 hit' process; the first hit being an inherited defect, the second hit leading to exostoses, and a third which occurs rarely leading to malignancy.

A second aspect of mosaicism in bone dysplasia relates to germ line involvement. It would appear that most mutations are in fact mitotic, thus as the embryo/fetus grows, mutations may occur and involve daughter cells. These can occur so early that they involve a large proportion of cells or at a later stage involving only a few cells. If the mutation and the daughter cells involve the germ line, there can be an increased risk for recurrences. This has been seen and documented in achondroplasia, pseudoachondroplasia, osteogenesis imperfecta, etc.

There are a number of identical twins in which one is affected with some type of bone dysplasia and the other is not. Clearly, this would represent a second cell line arising during the course of development.

Parent of origin affects, often called imprinting, have recently been recognized in which the phenotype depends on the sex of the transmitting parent. It would appear that male meiosis and female meiosis lead to different types of gene control. The effects of imprinting most often seen are related to growth and behavior. Growth factors, therefore, are at particular risk for being involved in parent of origin effects. Because there are likely to be a number of growth factors in bone it seems appropriate to look for parent of origin effects in the skeletal dysplasias. Pseudopseudohypoparathyroidism appears to be a disorder in which this type of parent of origin effects are seen.

Imprinting was recognized through the study of uniparental disomy. Uniparental disomy occurs when both chromosomes of a pair have come from one parent. One of the side products of uniparental disomy is that a disease may be expressed if both copies of the same chromosome which carries an abnormal recessive gene are inherited; thus a recessive disorder may occur in which only one parent is a carrier.

Many newly recognized mechanisms being described in genetics are likely to explain a variety of the unusual conditions which have been observed in the past. It is important to be aware of them in order to utilize new molecular techniques to properly trace genetic traits in various tissues.
CLINICAL-MOLECULAR CORRELATIONS IN THE SKELETAL DYSPLASIAS. 
David L. Rimoin, M.D., Ph.D., Daniel H. Cohn, Ph.D., and David Eyre, Ph.D. 
Medical Genetics, Cedars-Sinai Medical Center, UCLA School of Medicine, Los 
Angeles, CA and Department of Orthopaedic Surgery, University of Washington, 
Seattle, WA.

Numerous mutations in the type I collagen genes, COL1A1 and COL1A2, have 
been described in osteogenesis imperfecta (OI). A strong correlation has been 
established between the OI type I clinical phenotype and quantitative type I 
collagen defects. A gradient of increasing clinical severity as mutations 
approach the carboxyl-terminus of the helix for qualitative (structural) defects has 
been proposed, but significant exceptions to this generalization have been 
identified. More recently, mutations in the COL2A1 gene have been described 
in the spondyloepiphysyeal dysplasia (SED) family of disorders. The phenotypic 
spectrum among the type II collagenopathies is extensive, with phenotypes 
ranging from the neonatally lethal achondrogenesis II through the SED’s to 
Stickler syndrome and familial osteoarthropathy. We have studied cartilage type 
II collagen in over 60 patients with achondrogenesis II, hypochondrogenesis, 
SED and SEMD and the majority of them have electrophoretically detectable 
defects in type II collagen. In addition, we have found a direct correlation 
between phenotypic severity and the ratio of type I to type II collagen in cartilage. 
The type II collagen molecule appears to tolerate small changes in triple helix 
length: deletion of exon 20 or 48 or a partial duplication within exon 48 yield a 
moderate SED phenotype. Point mutations that result in substitution for a triple 
helical glycine residue appear to be the most common types of mutations within 
the SED family of disorders. Analysis of additional chondrodysplasia 
phenotypes may expand the type II collagenopathy spectrum, and 
characterization of additional mutations will allow determination of the 
relationship between genotype and phenotype.
EXTENDING THE NOSOLOGY OF THE CHONDRODYSPLASIAS TO THE
CELLULAR AND MOLECULAR LEVELS

WA Horton, MA Machado, J Ellard (Division of Medical Genetics, Department of
Pediatrics, University of Texas - Houston, Medical School, Houston, TX 77030)

The human chondrodysplasias have historically been named and classified
according to the phenotype they exhibit. These phenotypes have been defined by
clinical and radiographic features and to a lesser extent by the structure of the
skeletal growth plate where the mutations exert their adverse effects. With the
development of methods to evaluate the living cells and molecules that occupy the
growth plate, it has become possible to begin to define the phenotypes at this level.

We have utilized cell culture techniques to examine the characteristics of
chondrocytes from patients with chondrodysplasias. One group is characterized
by the elaboration of cartilage extracellular matrix that is deficient in volume and
structurally abnormal. Defects in the cellular processing, transport and
secretion of matrix molecules are often detected as illustrated by the mutations of
the type II procollagen gene that produce hypochondrogenesis and early to late
onset SED clinical phenotypes. In pseudoachondroplasia, processing defects are
detected, but the extracellular matrix that is secreted appears normal from
ultrastructural and limited biochemical analysis. In other disorders, such as
achondroplasia and thanatophoric dysplasia, the differentiation of chondrocytes
appears to be disturbed based on their cellular morphology and pattern of gene
expression. While this type of information is only beginning to emerge, it is clear
that it will have a major impact on how these disorders are viewed nosologically
as well as therapeutically.
CRANIOCERVICAL ANOMALIES IN OSTEOGENESIS IMPERFECTA GENETIC AND MOLECULAR CORRELATION

D. Sillence (The Children's Hospital, Camperdown NSW 2050, Australia)

Craniocervical anomalies, including basilar invagination, have hitherto been thought to be a rare complications of Osteogenesis Imperfecta. We have undertaken an extensive review of persons with OI ascertained through the Connective Tissue Dysplasia Clinic and the OI Society of NSW.

In 87 subjects reviewed with non-lethal types of OI, 25% were detected with basilar impression. Patients were screened with a single plain skull X-ray. All those with radiological evidence of basilar impression were reassessed with CT of the craniocervical junction with reconstruction of 1 mm cuts. Head MRI was performed for all patients with neurological symptoms or signs.

<table>
<thead>
<tr>
<th>OI TYPES</th>
<th>BASILAR IMPRESSION (Percent)</th>
<th>NEUROLOGIC SIGNS (Percent)</th>
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<tbody>
<tr>
<td>IA</td>
<td>10</td>
<td>0</td>
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<tr>
<td>IB</td>
<td>100</td>
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<tr>
<td>III/IV</td>
<td>30</td>
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<td>IVA</td>
<td>5</td>
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<tr>
<td>IVB</td>
<td>71.4</td>
<td>50</td>
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Three patients in this series have been referred for transoral clivectomy (Dr. Crockard, Humana Hospital, U.K.). Neurologic symptoms include cough, headache, paraesthesias and paraparesis. Neurologic signs include unusual forms of nystagmus such as convergence and down-beat nystagmus consistent with brain-stem compression. Acute hydrocephalus and severe unremitting trigeminal neuralgia are rare complications.

The vast majority of patients with OI Type I synthesise decreased amount of normal type I collagen, whereas patients with OI Type III/IV and IV synthesise decreased type I collagen but both normal and mutant collagens. There is an increased frequency of deformity of the spine in patients with OI type IVA and OI type IVB, suggesting a correlation between dominant negative mutations in type I collagen and basilar impression.
The concept of Bone Dysplasia Families suggests that phenotypically related chondrodysplasias are also pathogenetically related. It has been proposed that Stickler Dysplasia, Kniest Dysplasia and related disorders are members of such a family. It is characterized by a peculiar pattern of skeletal and facial abnormalities including myopia and cleft palate. We now present evidence that not only the milder (Stickler) but also the more severe (Kniest) phenotype are caused by defects of the COL2A1 gene.

Two families will be presented in which one parent had skeletal abnormalities compatible with a diagnosis of Stickler dysplasia and the child was diagnosed as Kniest dysplasia. In one family, analysis of the COL2A1 gene revealed a 28 bp deletion spanning the exon/intron boundary of exon 12. The deletion removed the highly conserved 5' splicing site of intron 13 and led to skipping of the whole exon 12 from the mature mRNA. The patient's mother with mild, Stickler-like changes was shown to represent a somatic mosaic for the mutation.

In the second family a transition of the highly conserved AG to GG and the 3' splicing site of intron 20 was found in the child leading to incorrect splicing. Again a mosaic status for this mutation was found in her father with the Stickler phenotype.

These findings confirm that Kniest dysplasia is caused by structural abnormalities of type 2 collagen and demonstrate that the mosaic state of the underlying mutation may result in a Stickler phenotype. They validate the family concept. Pattern recognition helps to establish a pathogenetically oriented nosology of bone dysplasias and may assist in the future biochemical and molecular analysis of rare bone dysplasias.
SPONDYLO-METAPHYSEAL DYSPLASIA

K. Kozlowski (The Children's Hospital, Pyrmont Bridge Road, Camperdown Sydney, 2050 Australia)

Spondylo-metaphyseal dysplasias comprise a group of diseases in which the spine and the metaphyses of the tubular bones are affected. Spondylo-metaphyseal dysplasia with minimal metaphyseal changes is called brachyolmia.

There are two well differentiated and relatively common types of spondylo-metaphyseal dysplasias - the common type and the Sutcliffe (corner fracture) type.

Several types of brachyolmia are recognized.

The radiographic examination is the only method which can recognize the disease.

The clinical findings and histology are nondiagnostic.
MESOMELIC AND ACROMESOMELIC BONE DYSPLASIAS

L.O. Langer, Jr. (University of Minnesota, Minneapolis, Minnesota)

These are conditions in which the distal and/or the middle segments of the limbs are disproportionately short.

There are a number of short-limb dwarf conditions which fit this description. In some conditions the same segment is not always the shortest. In these conditions no mention is made in the name of the bone dysplasia which alludes to mesomelia or acromesomelia.

Generally speaking, the bone dysplasias in which the terms mesomelic or acromesomelic are used in the name of the entity have marked shortening of these segments. Conditions commonly referred to as mesomelic dysplasias include the Langer type, the Nievergelt type, the Robinow type, the Campailla-Martinelli type, the Rheinhardt-Pfeiffer type and dyschondrosteosis. The acromesomelic dysplasias included the Maroteaux, Martinelli, Campailla type, the Grebe type and the Hunter-Thompson type.

The diagnostic radiographic features will be illustrated and the clinical and genetic features will be commented upon briefly.

That mesomelic dysplasia, Langer type, does not necessarily represent homozygous dyschondrosteosis will be discussed.
CRANIOTUBULAR DYSPLASIAS. R.J. Gorlin, Department of Oral Science, University of Minnesota, Minneapolis, U.S.A.

In 1969, Gorlin, Spranger and Koszalka divided craniotubular dysplasias into Pyle disease, craniometaphysial dysplasia, craniophyseal dysplasia, frontometaphysial dysplasia, Schwarz syndrome, craniometaphysial dysplasia, dysosteoosclerosis, and oculodentoosseous dysplasia. Cranio-
tubular hyperostoses consist of Van Buchem disease, sclerosteosis, congenital hyperphosphatasia, autosomal dominant osteosclerosis and Camurati-Engelmann disease. These and other newer disorders will be discussed.
FIBROUS DYSPLASIA AND MYXOMAS

P. Maroteaux, M. Le Merrer (Hospital des Enfants-Malades, Paris)

A 48-year-old man, affected by fibrous dysplasia, was referred at the consultation for two tumors on the thigh and left leg, which were developed during the last months.

When he was 18 (years-old), the fibrous dysplasia was detected at the same time as a femora fracture. Twenty years later, a lytic lesion on the calvarium was found by a systematic radiography. Finally, a spontaneous fracture of the right ankle appeared in the course of this last year.

During the examination, the large and tough tumors infiltrating the back side of the right thigh and the left leg were found and there was a parieto-occipital depression on right side of the skull.

The X-rays examination showed typical changes of fibrous dysplasia, with multiple lytic areas on the two humerus, radius, femurs, tibiae and fibulas. On the skull which was irregular and thickened, there was a large defect on parieto-occipital localization.

The ultrasound examination of the swelling on the thigh showed many round and irregular cysts, often "hyperechogenic" of compartmentalized.

On the RMN examination these tumors appeared bulky, homogeneous with partitions. The diagnoses of fibrous dysplasia is very obvious as illustrated by the aspect of long bones and skull images both of them demonstrated; patchy area of lysis with blurred aspect. The swelling on the legs seemed to be identical to multiple intramuscular myxomas which had been described earlier (Enzinger, 1965; Wirth, 1971; Roze, 1967; Lejeune, 1972).

The association of a fibrous dysplasia and multiple intramuscular myxomas seemed to be reported a long time ago (first publications in 1926) and consistent with a specific affection, which is always sporadic.

References


PUNCTATE EPIPHYES: A RADIOLOGIC SIGN NOT A DISEASE

A.K. Poznanski (The Children's Memorial Hospital, Northwestern University, Chicago, IL 60614)

CAUSES OF PUNCTATE (STIPPLED EPIPHYES):

1. Chondrodysplasia punctata (CDP)
   a. X-linked dominant (Conradi-Hunermann) - Usually asymmetric short limbs - Ichthyosis which improves postnataally - Cataracts - Puncta usually extensive - Hand polydactyly may be seen - Occurs only in girls
   b. Autosomal recessive (rhizomelic CDP) - A peroxisomal disorder - Usually symmetric shortness particularly the humeri - Cataracts - Neurologic degeneration with poor prognosis - Puncta are less extensive than in x-linked dominant - Coronal clefts in vertebrae - Delayed myelination
   c. X-linked recessive - Radiologic findings not well defined
   d. Mesomelic-metacarpal type CDP = Tibia-metacarpal type (Rittler, Menger, and Spranger) - Includes: Mesomelic dysplasia type (Burck) - Humero-metacarpal type (Borochowicz) - Flat face and nose - Short bones includes: Metacarpals, tibias, ulnas, and humeri - Mild stippling - Coronal vertebral clefts
   e. Brachytelephalangic type (BTP, CDP) (Maroteaux) - Facial dysmorphism - very small nose - Short distal phalanges - Other phalanges may be affected - Fine puncta, not extensive - ? X-linked recessive - ? overlap with Sheffield form - Radiologically similar to Warfarin embryopathy
   f. Sheffield type - Mild - Probably mixed group - Some cases with short distals had nasal abnormalities - Very similar to brachytelephalangic type - Other may have been tibia - Metacarpal type
   g. Pacman dysplasia (Shohat, Rimoin, Gruber, Lachman) - Stippling in many areas - Bowed short bones - Periosteal cloaking - Osteoclasts with "Pacman" appearance
   h. Other atypical types (Lawrence et al.) - Unilateral case - Absent femora case - Single hand ray involved case - Cone epiphyses case - BTP type - Severe mesomelic case

2. Zellweger syndrome (cerebrohepatorenal syndrome) - A Peroxisomal disorder - Severe hypotonia - Characteristic facies - Patellar puncta prominent - Less puncta elsewhere - Club foot deformity - Cystic changes in kidneys
3. Disorders acquired in utero

a. With short distals - Warfarin embryopathy - Tracheal calcification is common - The puncta and growth abnormalities are not due to hemorrhage but to the teratogenic action of Warfarin

b. Involving primarily the tarsals - Alcohol - Hydantoins - Phenacetin - Febrile illness - Rubella

4. Other genetic or congenital abnormalities (mainly tarsal puncta) - Absence defects - Acrodysostosis - Cerebro-costo-mandibular syndrome - C.H.I.L.D. syndrome - D-B translocation - Dysplasia epiphysealis hemimelica - GM-1 gangliosidosis - Metachondromatosis - Mucolipidosis 2 - Smith-Lemli-Opitz syndrome - Trisomy 18 and 21 - Vitamin K epoxide reductase deficiency

Puncta can be seen in a variety of unrelated disorders. The pattern of puncta can sometimes be useful in diagnosis e.g. puncta predominantly in patella suggests Zellweger syndrome. Puncta affecting primarily the calcaneus or talus may be seen in a variety of unrelated conditions includes Trisomy 18 and 21, fetal alcohol, DeLange syndrome, mucolipidosis 2 etc.

Puncta usually disappear by 5 years of age; therefore, diagnosis of various syndromes with puncta becomes more difficult in older children when only the deformity at the site of the puncta remains. A complete skeletal survey in infancy including hands and a lateral view of the feet is very helpful for diagnosis if Zellweger is questioned lateral view of the knees may be of value.

The presence of puncta is associated with growth disturbances in the skeleton. There is delay in appearance of ossification centers, decreased growth of affected bones, small carpal bones, angulation of affected bones, and cartilaginous rests in the metaphysis which can also cause deformity. Cartilage outside of the skeleton is also affected resulting in a small nose and lack of tracheal growth particularly when the cartilage is calcified. In the rat treated with warfarin and vitamin K1 a short nasal septum was seen which was related to calcification. Whether this also occurs in humans is not clear.

Brain abnormalities are seen in both the disorders of peroxisome that have puncta. These are Zellweger syndrome and the recessive chondrodysplasia puncta. MR is the best approach for their evaluation.
SPONDYLOCARPOTARSAL FUSION SYNDROME - A NEW AUTOSOMAL RECESSIVE CONDITION. R.J. Gorlin¹, L.O. Langer, Jr.², D. Donnai³.
¹Department of Oral Science, University of Minnesota, Minneapolis, U.S.A.
²Department of Radiology, University of Minnesota, Minneapolis, U.S.A.
³Regional Genetic Service at St. Mary's Hospital, Manchester, England.

A syndrome of progressive scoliosis due to unilateral unsegmented bar, carpal and tarsal fusion, flat feet, cleft palate, cervical vertebral fusion, and sensorineural hearing loss appears to have autosomal recessive inheritance. We had opportunity to see several examples. Search of the literature revealed a few affected sib pairs reported under different names. Parental consanguinity was found (Langer and Moe, 1975; Ventruto and Catani, 1986).

Our first patient was a short somewhat disproportionate female with corrected scoliosis, flat feet, and sensorineural hearing loss. She has been a gymnast but had trouble bending her wrists. An early wrist film for bone age determination showed carpal bone fusion. Recent examination exhibited tarsal fusion.

Our second and third patients were sibs with similar anomalies including scoliosis, capitate-hamate fusion, clinodactyly of fifth fingers, cleft palate, and hearing loss.

We propose the name spondylocarpotarsal fusion syndrome for the disorder.
A NEW SYNDROME OF DELAYED OSSEOUS MATURATION SHORT STATURE AND CARDIAC ANOMALIES

R. Olge, K. Kozlowski, D. Sillence (The Children's Hospital, Camperdown, NSW 2050, Australia)

Two siblings presented with hyperbilirubinaemia and cardiovascular anomalies detected in the newborn period. Skeletal survey showed an unusual pattern of skeletal anomalies. Both have large heads. The older sibling, presently aged 7 years, had a large anterior and posterior fontanelle, prominent frontal regions and a triangular shaped face. Linear growth velocity was normal although she remains on the third percentile for height. A younger male sibling aged 2 years had identical features.

The skeletal survey at birth showed a wide anterior and posterior fontanelle with a large parietal foramen and delayed ossification of the ischio-pubic rami. Subsequent skeletal surveys have shown thin small tubular bones in the hands with shortening of metacarpals. The bone age is delayed and there is mild osteopenia.
A DISTINCT FORM OF SPONDYLOPEPTOPIPHYRELL SYMPHISIA WITH DISLOCATIONS


Two unrelated patients with identical radiological features are presented. Hypoplasia was noted at birth and one patient was diagnosed as having congenital fibre-type disproportion in the neonatal period. Later muscle biopsies however were entirely normal. Both patients, now in their teens, are of normal intellect but have multiple large joint dislocations, which are particularly incapacitating at the knees.

PRESENTATIONS
June 17, 1993
June 18, 1993
A DISTINCT FORM OF SPONDOLOEPIMETAPHYSAL DYSPLASIA WITH DISLOCATIONS


Two unrelated patients with identical radiological features are presented. Hypotonia was noted at birth and one patient was diagnosed as having congenital fibre-type disproportion in the neonatal period. Later muscle biopsies however were entirely normal. Both patients, now in their teens, are of normal intelligence, show striking epiphyseal and metaphyseal changes of the long bones and have multiple large joint dislocation, which are particularly incapacitating at the knees.
SPONDYLOEPIMETAPHYSEAL DYSPLASIA
CAUSED BY A GLY → ARG MUTATION IN TYPE II COLLAGEN

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²Collagen Research Unit, Biocenter and Department of Medical Biochemistry,
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³Helsinki University Hospital, Department of Medical Genetics, Helsinki, Finland

A mutation was identified in the area coding for the amino terminal part of the
triple helix of type II collagen in a sporadic patient with spondyloepimeta
physisal dysplasia (SEMD). The patient was a 16-year-old boy, who was normal in birth
measurements, but had short limbs and neck. By the age of 4 months growth was
retarded below 2 SD of the mean for his age. Severe bowing of the lower extremities
and deep lumbar lordosis developed during the first years of life and skeletal radiographs
showed platyspondyly and both metaphyseal and epiphyseal abnormalities. The patient
had normal vision and hearing and no cleft palate. Previously, three mutations in the
area coding for the carboxyl terminal end of the triple helix have been reported to result
in SED. This novel mutation demonstrates that amino acid substitutions in the amino
terminal part of the type II collagen triple helix results in SEMD.
COMPARATIVE MORPHOLOGICAL INVESTIGATIONS ON THE SED-CONGENITA FAMILY.

H. Stoess¹, J. Spranger², B. Pontz³
¹ Institute of Pathology, University, D 8520 Erlangen, BRD
² Children's Hospital, University, D 6500 Mainz, BRD
³ Children's Hospital, University, D 8000 München, BRD

On the basis of comparative radiological and clinical investigations achondrogenesis type II, hypochondrogenesis and the SED congenita, should be classified together in a single group of diseases, the SED congenita family. Biochemical and molecular biological investigations have shown that all three entities are based on a defect in type II collagen. For this reason, these entities may be considered as manifestations of varying severity of a single biochemical defect. Comparative morphological studies in achondrogenesis type II, hypochondrogenesis and SED congenita reveal similar morphological characteristics for all three entities. In accordance with the differences in retardation of bone development, differences in the disordering of the growth plate are found. Cartilage canals are found to persist not only in the cartilage of achondrogenesis type II and hypochondrogenesis, but also in that of SED congenita. In all three entities, electron microscopy reveals very thin collagen fibrils, which, however, are reduced to a variable degree. In analogy to the clinical differences in severity of this disease group, certain morphological characteristics are found to depend upon the severity of manifestation of the disease. The structure of the growth zone may correlate well with the different clinical degrees of severity of achondrogenesis type II, hypochondrogenesis and SED congenita.
GLYCINE TO ALANINE SUBSTITUTION IN THE TYPE II COLLAGEN OF A PATIENT WITH HYPOCHONDROGENESIS

J. Bonaventure1, P. Ritvaniemi2, P. Freisinger1, D. Leguellec3, S. Franc2, L. Ala-Kokko2 D.J. Frochop1 and P. Maroteaux1

1 CNRS URA 584, Hôpital Necker, Paris. 2 Collagen Research Unit Dept of Medical Biochemistry, University of Oulu, Finland. 3 Institut Chimie des protéines Lyon, France. 4 Dept of biochemistry and molecular biology, Jefferson Medical college, Philadelphia, USA.

We have studied a 38 week-old fetus with hypochondrogenesis, a lethal chondrodysplasia with short-limbed dwarfism and underossified vertebrae. Electron microscopy of articular cartilage illustrated chondrocytes with a dilated rough endoplasmic reticulum. Immunohistologic studies of cartilage revealed the presence of abundant vascular canals which stained intensively with a polyclonal antibody to type I collagen. This component was also found in the extracellular matrix of pathological chondrocytes and was associated to a relative decrease in collagen type II amount. Consistent with these observations was the demonstration by electrophoretic analysis of the presence of both type I and II collagens in pepsin-soluble material extracted from cartilage.

Most of the α1(II) chains of type II collagen had an abnormal electrophoretic mobility suggesting heterozygosity for a defect in the triple helical domain. Cyanogen bromide mapping located the mutation in the α1(II) CB10.5. The DGGE technique was used to identify a single base change in exon 35 which by direct sequencing of PCR fragments was shown to correspond to a G → C transition in the second base of the first codon. The mutation converted the codon for glycine α1-604 to an alanine codon. This mutation is likely to be sporadic since parents were phenotypically normal and had four healthy children. It had no effect on the thermal stability of α1(II) chains but rotary shadowing analysis of collagen fibrils demonstrated a large variability in their size. We suggest that overmodified collagen type II molecules in addition to collagen type I interfere with the normal assembly of stable fibrils in the tissue.
CLINICAL AND RADIOLOGICAL FEATURES OF SKELETAL DYSPLASIAS LOCALIZING TO THE LONG ARM OF CHROMOSOME 12

C.M. Hall, D.G. Shaw (The Hospital for Sick Children, Great Ormond Street, London WC1N 3JH, England)

The locus for Type 2 collagen alpha-1 (COL2A1) has been assigned to 12q13.1 - 12q13.2. This collagen, also called cartilage collagen, occurs in the vitreous and is also represented in the inner ear.

A defect in COL2A1 has been found in achondrogenesis Type Langer-Saldino, spondyloepiphyseal dysplasia congenita and spondyloepimetaphyseal dysplasia Type Strudwick. Chondrocalcin is a calcium-binding protein, a C-propeptide which is important in forming the triple helix of Type 2 collagen. This is abnormally processed in Knies't disease. In addition linkage analysis indicates that the Type 2 collagen gene is the site of the mutation in Stickler's syndrome.

The spectrum of clinical and radiological changes in the skeletal dysplasias linked with the COL2A1 locus on chromosome 12 will be illustrated.

Other similar conditions will be discussed.
Immunolocalization of interstitial collagen types in bone and cartilage from two patients with severe, lethal Achondrogenesis type I

We report here on two fetuses from the same mother delivered in the 18. and 19. week of gestation, resp., after consented abortion who presented with severe micromelia, lack of vertebral ossification, severe hypoplasia of the ossa ilii and extensive histomorphological abnormalities of the cartilage, so that the diagnosis of severe, lethal achondrogenesis type IB was presumed. At autopsy, no internal malformations were noted. Tissue samples from different regions of the skeleton were embedded into paraffin and used for the immunolocalization of collagens I, II, III, IV, V, VI and X. The chondrocytes which showed morphologically occasionally intracytoplasmatic PAS-positive inclusions were surrounded by a sparse matrix which consisted of collagens I, III, V, VI and X to varying extent. Collagen IV (basement membrane collagen) was not seen within the cartilage. Intracellularly, a positive collagen II staining was seen in most chondrocytes. On the ultrastructural level, the cartilage cells contained a cystically enlarged endoplasmatic reticulum filled with occasional fine-fibrillar material. The adjacent bone showed a regular distribution of collagens.

Our observations demonstrate an "anarchic" composition of the cartilage matrix in these two cases of achondrogenesis type I with almost all collagen types present in the pericellular matrix (except for the basement membrane collagen IV). The intracytoplasmatic staining for collagen II - which may represent the PAS-positive material within the chondrocytes with the enlarged endoplasmatic reticulum - may be a correlate for a defect in this collagen type which may render the collagen II difficult to be secreted into the extracellular matrix.
PHENOTYPIC EXPRESSION OF CHH GENE RESPONSIBLE FOR CARTILAGE-HAIR HYPOPLASIA
I. Kaitila, O. Mäkitie and T. Sulisalo (Departments of Medical Genetics, Helsinki University Hospital and University of Helsinki, SF-00014 Helsinki, Finland)

The autosomal recessive cartilage-hair hypoplasia (CHH) or metaphyseal osteochondrodysplasia, McKusick type, results in short-limbed short stature, sparse and fine hair, joint laxity and, on occasion, Mb. Hirschsprung. In most Caucasian populations CHH is rare, whereas there are more than 100 patients among the Old Order Amish in the U.S. and among the Finns (McKusick et al, 1965; Mäkitie, 1993). Based on clinical, biochemical, radiographic and genetic studies on 47 male and 65 female Finnish patients, aged range from 10 months to 52 years, we established growth curves for CHH, analysed growth parameters, skeletal abnormalities and intrafamilial variation, confirmed cell-mediated immunodeficiency and risk of malignancies, and observed hypoplastic anemia. The basic biochemical defect and pathogenesis are unknown. The clinical features and laboratory findings suggest a fundamental pleiotropic defect in the regulatory mechanisms of cellular proliferation. As the first step to define the molecular defect we have mapped the Finnish CHH gene to chromosome 9 by genetic linkage analysis (Zmax 6.89 at theta max 0.02). This finding has been used twice for early prenatal diagnosis.

Mäkitie J Med Genet, in press.
A PATIENT WITH UNUSUALLY SEVERE RADIOGRAPHIC AND PHYSICAL
MANIFESTATIONS OF CLEIDOCRANIAL DYSOSTOSIS

M. Irons and R.G.K. McCauley (The Boston Floating Hospital, New England Medical Center,
Tufts University School of Medicine, Boston, MA 02111)

Cleidocranial dysostosis is a bony dysplasia characterized by clavicular abnormality,
delayed ossification of the fontanelles, and an increased transverse diameter of the cranium. Over
100 associated anomalies have been described.

Our patient was noted at birth to have an excessively large fontanelle, clavicular absence
bilaterally, hypertelorism, and bilateral hip dysplasia. The diagnosis of cleidocranial dysostosis
suggested by the clinical presentation was confirmed by skeletal survey.

In addition to the typical features seen, our patient has unusual radiographic findings and
medical problems more severe than usually seen in this disorder. The unusual medical features
include a seizure disorder, developmental delay, sleep apnea requiring tracheostomy placement,
and restrictive lung disease secondary to severe kyphoscoliosis and chest wall deformity.

Her unusual radiographic findings include the following: early severe under-ossification of
the calvarium, spine and pelvis severe enough to simulate achondrogenesis in the cervical spine, a
unique linear pattern of ossification in the cervical spine, an unusual spotty pattern of ossification
in the lower spine, and anterolateral bowing of the femora with pseudoarthrosis on the left at birth.

These features, both radiographic and medical, extend the spectrum of abnormalities seen
in cleidocranial dysostosis and may help define the severity of the disorder.
A new sclerotic bone dysplasia in two Japanese siblings born to first degree cousin parents is reported.

The disease is characterized by early developmental delay and hypotonia. The facies and the teeth are normal. No cranial nerve palsy is observed. The older sister was lost to follow up at the age of 11 months. She was of normal height. The brother showed short stature and developed later spastic paraplegia and epilepsy. The only abnormal laboratory finding was increased alkaline phosphatase.

The radiographic examination showed metaphyseal undermodeling with sclerosis, epiphyseal, acetabular, glenoid sclerosis, peripheral sclerosis of the flat bones and vertebrae, diaphyseal osteopenia and clavicular hypoplasia. The skull was normal and there was no platyspondyly. There was no increased bone fragility.

Some of these features overlap with those of dysostosesclerosis.
OSTEOPATHIA STRIATA WITH CRANIAL SCLEROSIS

B.B. Gay, Jr., L.J. Elsas, J.B. Wyly (Egleston Children's Hospital, Emory University, Atlanta, GA 30322)

Osteopathia striata with cranial sclerosis (OS-CS) is a specific bone dysplasia manifested by hypertelorism, flat nasal bridge, frontal bossing, large head, hypoplastic maxilla, palate anomalies, chronic otitis media, hearing deficits, nasal obstruction, and neurological changes of deafness, facial palsy, ophthalmoplegia, and mental retardation. We will review the clinical and radiologic findings in a new patient from birth to 20 years; this is believed to be the thirty-second patient reported. OS-CS is 2.5 times more common in females and occurs sporadically or as an autosomal dominant condition with patients presenting for evaluation from the newborn period to the fifth decade. Skeletal abnormalities are distinctive including sclerosis of the skull base and calvarium, linear striated densities in the long bones and pelvis, and poor development of the mastoid and sinus air cells. Radionuclide bone scans with SPECT indicated in our patient increased bone turnover which was supported by biochemical findings of increased pyridinoline excretion. The major complications are due to constriction of essential foramina at the skull base. The condition is not life-threatening but can produce disability.
FAMILIAL HYPOCALCIURIC HYPERCALCEMIA MIMICKING SKELETAL DYSPLASIA

B.D. Hall, C.C. Mabry (Department of Pediatrics, University of Kentucky, Lexington, KY 40536-0284)

Familial hypocalciuric hypercalcemia (FHH) is a rare metabolic disorder capable of mimicking skeletal dysplasias. It can be confused with thoracic dystrophy, hypophosphatasia, osteogenesis imperfecta, and rickets. FHH is frequently misdiagnosed as neonatal hyperparathyroidism. The most frequent radiological feature of FHH is generalized bone demineralization, however, some patients have associated metaphyseal defects and rib cage deformities.

We report 2 Black siblings with FHH whose father and paternal uncle also had hypercalcemia. The 35 week male sibling was considered normal until a babygram at 5 days showed generalized demineralizations, small, thin, ribs, small chest, and widened metaphyses. His sister, born 1 1/2 years later, had a small deformed chest, respiratory distress, and similar skeletal findings. Both had elevated parathyroid hormone and hypocalciuric hypercalcemia. By 1 to 1 1/2 years, the skeletal findings had reverted to normal.

FHH clearly can have adverse prenatal effects on bone mineralization with concomitant metaphyseal and rib defects. However, it may go unrecognized with minimal sequelae as seen in the father and paternal uncle. In the young infant, the diagnosis can be confused with many skeletal and metabolic disorders. FHH is usually a benign condition because of its low grade hypercalcemia and lack of renal involvement. Persistent chest deformity did occur in our female patient. FHH should be considered in any individual with unexplained generalized bone demineralization.
RESTRICTIVE LUNG DISEASE AND ORAL DYSPRAXIA IN KNIEST DYSPLASIA

M. Irons (The Boston Floating Hospital, New England Medical Center, Tufts University School of Medicine, Boston, MA 02111)

Kniest dysplasia is a generalized bony dysplasia with characteristic craniofacial, orthopedic, and skeletal abnormalities. While other anomalies involving the palate and eye, as well as hearing loss are commonly seen in affected patients, a decrease in thoracic volume and feeding abnormalities have not been reported.

Our patient presented with the clinical and radiographic features of Kniest dysplasia at birth. In addition to the usual features seen, he was also noted to have restrictive lung disease secondary to an unusually small thorax. Clinically this presented with significant tachypnea with respiratory rates of 60-80, mild hypercarbia, and decreased oxygen saturation. The tachypnea also interfered with oral feeding so that nasogastric feedings were required.

Supplemental oxygen delivered by nasal cannula was required until two years of age when growth of the thoracic cavity was finally adequate for maintenance of normal respiration. The patient also developed a feeding disorder manifested by an oral dyspraxia which necessitated placement of a gastrostomy tube for nutritional support.

The clinical features of restrictive lung disease due to a small thoracic cavity and oral dyspraxia leading to a feeding disorder in this patient extend the spectrum of problems that can be seen in patients with Kniest dysplasia.
The Femoral Hypoplasia - Unusual Facies Syndrome in 4 Generations

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Department of Pediatrics (MR and AV) and the Ultrasound Center (JS), Wright State University, School of Medicine, Dayton, OH

The genetics of the femoral hypoplasia - unusual facies syndrome (McKusick 134780) has been uncertain. Most cases have been sporadic; some have occurred in infants of diabetic mothers. An affected father and daughter have been reported by Lampert (Clin Genet 17:255-258, 1980) and an infant and maternal great-aunt were described by Kelly (Birth Defects Orig Art Ser X (12) 508-509, 1989).

During a routine prenatal ultrasound examination the fetus was found to have short femora and a small mandible. At birth, the infant girl showed the characteristic features of the syndrome, i.e. small size, short mildly bowed femora, cleft palate and characteristic facies (short nose, long philtrum, small pointed chin). The father, 2 paternal uncles, the paternal grandmother and the paternal great-grandfather were affected. A brother of the grandmother had died in childhood. He had been very short and had had a cleft palate. The father, an obligate heterozygote, was short (160 cm) but had neither femoral hypoplasia, unusual facies or cleft palate.

It seems that there is at least one variant of the syndrome that is inherited as an autosomal dominant with incomplete penetrance.

Pedigree, ultrasonograms, photographs and radiographs will be presented.
BOWING OF THE LEGS WITH METAPHYSEAL INVOLVEMENT: AN EMPHASIS ON DIFFERENTIAL DIAGNOSIS AND A SPECIAL CONSIDERATION TO SCHMID TYPE METAPHYSEAL CHONDRODYSPLASIA (SMCD)

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Bowing of the legs is a relatively common manifestation of skeletal dysplasias. In the past, bowed legs often implied rickets. Currently, besides physiologic bowing of infancy and familial congenital bowing, SMCD is a common cause of mild and moderate bowing of the legs. We wish to report here our personal observation on SMCD, two isolated cases and a family with 3 affected individuals in 3 generations assessed within the past year and to review on the differential diagnosis of bowing of the legs with primarily metaphyseal involvement.

Diagnosis of SMCD is often missed because bowed legs, genu varus, waddling gait, and short stature usually do not manifest before 2 years of age and because pregnancy, delivery, birth length, weight, head circumference, intelligence and clinical laboratory values (calcium, phosphorous, magnesium, 25-hydroxy vitamin D, PTH, and quantitative plasma amino acids, and chromosomes) are normal. However, urinary phosphoethanolamine excretion may be normal or low and alkaline phosphatase may be slightly elevated.

Definitive diagnosis is based on radiographic findings of bowing of distal femora, metaphyseal flares at the distal femora and proximal tibia, coxa vara, genu vara, increased density of provisional zone of calcification, anterior cupping of the ribs, and relatively normal upper limbs and spine. Differential diagnosis of non-lethal types of bowing of legs with metaphyseal involvement should include Weismann-Netter syndrome, campomelia, mesomelic dysplasia, hypophosphatasia, vitamin D dependent and resistant rickets, metaphyseal acroscyphodysplasia, metaphyseal anadysplasia, kyphomelic dysplasia, metatropic dysplasia, Kniest dysplasia, dyssegmental dysplasia, spondylometaphyseal dysplasia, and especially other types of metaphyseal chondro dysplasias (cartilage hair hypoplasia, Schwachman syndrome, Jansen type, and Spahr type). We suspect, based upon our experiences, that a substantial proportion of SMCD remain undiagnosed.
FIVE MEMBERS IN THREE FAMILY GENERATIONS WITH METAPHYSICAL DYSTOPHOSIS SCHMIDT

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Fourteen years old boy with disproportionate short stature was found to present metaphysial dysostosis Schmidt. His two sisters, aged 6 and 16 years exhibited the same features of short stature and dysplasia. His 4 years old brother was apparently healthy. Their father, his brother and their mother are found to have the same stigmata. The children's stature deviated 3-4.5 SD below the height for age and sex. Waddling gait was present (severe in one sister and the boy, moderate in the father and in the other sister). Abduction of the hips was limited. The boy and the older sister presented bilateral flaring of the lower rib cage. Roentgenographic changes were: irregularity, widening, fragmentation of distal tibial and fibular metaphyses. There was moderate delay in bone maturation (1-2 years), and epiphyseal centers were normally formed and mineralized.

Normal serum values for calcium, phosphorus, alkaline phosphatase, and urine excretion of those minerals are found. Acid-base balance, creatinin in serum, mucopolysaccharides in urine were normal. Karyograms were within the norm.

An autosomal dominant inheritance is demonstrated in this family (penetrance lacked in one boy).
A POSSIBLE CASE OF DESBUQUOIS SYNDROME: HOMOGENEITY OR HETEROGENEITY?

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The male proband was born as the second child of healthy, consanguineous parents. The first child was healthy. Gestation was complicated by growth retardation. Spontaneous delivery in a breech presentation took place at 37 weeks gestation. Mild perinatal asphyxia was present. Birth weight was 1900 g, length 37 cm and OFC 32.5 cm. Upon examination he had a short-limb, rhizomelic, dwarfism. His eyes protruded and he had a flat face. The thoracic cage was short and slightly narrowed in the upper half. Radiography revealed broad metaphyses and luxations of radii and knees. Bone ages of hands and feet were advanced. Radiography of the vertebral column showed narrowing of the intervertebral spaces, high lumbar vertebrae and stippling of thoracolumbar vertebral arches. The child had persistent respiratory problems of which he died at the age of 3 months. Autopsy was refused. The clinical and radiological features of this child were very similar to those of a case previously published by us (Beemer et al., Am.J.Med.Genet.1985;20:555-558). Both cases could be a severe representation of the Desbuquois syndrome or constitute a separate entity which will be discussed.
HETEROGENEITY IN CHONDRODYSPLASIA PUNCTATA

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The chondrodysplasia punctata (CDP) syndromes comprise a heterogeneous group of congenital bone dysplasias - all characterized by microcalcifications in vertebral, pelvic and limb metaphyseal cartilage until later infancy and by brachymelia and hypoplasia of the midfacial region. At least 5 monogenic CDP entities have been delineated: a rhizomelic CDP (autosomal recessive), an X-linked dominant CDP, an X-linked recessive CDP, a CDP of Sheffield type with a relatively light phenotypic expression and a tibia-metacarpal type of unclarified inheritance.

We report 5 fetuses and preterm babies with CDP. In two fetuses the autosomal recessive rhizomelic form could be diagnosed on the basis of peroxisomal enzyme defects. Both showed rhizomelic brachymelia - but with a striking difference in severity. Focal ichthyotic skin changes in a pattern compatible with clonal X-linked inactivation and asymmetric brachymelia led to the diagnosis of the X-linked dominant form in a female preterm baby. X-linked recessive CDP was suggested in a stillborn boy with rhizomelic, normal peroxisomal activity, characteristic very flat nose with lateral grooves and distant brachytelephalangy. Extremely severe CDP changes, short ulnar metacarpal bones, short and dysplastic tibial bones and proximal dislocation of the radial bones suggested presence of the tibia-metacarpal type of CDP in a 27-week-old male fetus.

The presented cases illustrate that subclassification of CDP using morphological, radiological and biochemical criterias is possible - especially in fetuses and preterm babies where the phenotypic picture appear to be more distinct and clear-cut than in fullborn babies and infants.
Maternal systemic lupus erythematosus (SLE) and chondrodysplasia punctata in two infants. Coincidence or association?

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Chondrodysplasia punctata is seen in a heterogeneous group of disorders, including some teratogenic exposures. It has been reported with exposure to Warfarin, Dilantin and alcohol as well as rubella embryopathy. To our knowledge an association with maternal autoimmune disease has not been documented. We report 2 unrelated infants whose mothers had SLE who had stippled epiphyses in the context of very different clinical pictures. The first patient, a premature female (29 wks gestation), was discovered incidentally to have stippling of the proximal femoral epiphyses in the newborn period. A full skeletal survey revealed additional stippling in the heel area. Follow-up studies at 5 months of age (2 months, corrected) showed resolution of the femoral stippling. She developed the typical rash of neonatal lupus at 2 1/2 months of age (term, corrected) which subsequently resolved. She has otherwise been well and is developmentally appropriate at one year of age. The mother, who is positive for anti-Ro and anti-La antibodies, was treated with prednisone throughout the pregnancy. The second child, a male born at 36 wks gestation, was noted to have stippled epiphyses during investigations for a severe static encephalopathy characterized by hypotonia and multiple contractures. Radiographs in the newborn period showed coronal clefing of the cervical and upper thoracic spine and stippling in the shoulder and hip areas; these were still present at 6 months of age. The karyotype and levels of very long chain fatty acids were normal. No imaging studies of the brain were carried out. He died at 6 months of age; no autopsy was done. The mother was treated during the pregnancy with verapamil and prednisone, and had taken azathioprine prior to conception. These cases raise the possibility of a direct relationship between maternal SLE and chondrodysplasia punctata. We plan to investigate this by prospectively studying infants of mothers with SLE.
THE "ELEPHANT'S LEG DYSPLASIA": A NEW MESOMELIC AND ACROMELIC SHORT LIMBED DWARFISM.

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A new short limbed dysplasia with particular involvement of the hands, feet and the lower legs in a twelve year old boy is described. In addition to the shortening there was marked thickening of the tibia. The epiphyses were large and appeared cone shaped in the hands. There was brachydactyly, polydactyly and syndactyly of the hands and feet. The metaphyses of the long bones showed irregular ossification. Spinal canal stenosis at the lumbar spine level required laminectomy.

In addition to the skeletal features there was tortuosity and sacculation of the anterior urethra and a midline cleft lip. The child had chronic middle ear disease and was developmentally delayed.

The unique and differentiating features of this new skeletal dysplasia will be discussed and illustrated.
A DE NOVO 17Q PARACENTRIC INVERSION MOSAICISM IN A PATIENT WITH BEEMER-LANGER TYPE SHORT RIB-POLYDACTLY SYNDROME

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The short rib-polydactyly syndromes (SRPS) are a heterogeneous group of lethal skeletal dysplasias. Beemer et al (1983) described a new form of SRPS, reminiscent of type II Majewski syndrome without polydactyly. Yang et al first suggested the term “Beemer short rib syndrome” in 1987 and later in 1991 recommended the eponym “Beemer-Langer” and used the abbreviation SR(P)S to indicate infrequent manifestation of polydactyly. We wish to report a patient with Beemer-Langer type SR(P)S with a de novo 17q paracentric inversion mosaicism. The observation of this chromosome association leads us to speculate that the disruption of the critical sites of two structural genes Hox-2 and COL1A1 located near the paracentric inversion break sites can lead to variable phenotypes of lethal skeletal dysplasias which include Beemer-Langer type of SR(P)S.

The pregnancy of 20 weeks of gestation was terminated because of multiple abnormalities detected by prenatal ultrasonography. The mother was a 21-year-old Gravida III Para I and Abortion I white female. At 17 weeks of gestation, ultrasonography revealed biparietal diameter (19 weeks), tibia (14 weeks), fibula (15 weeks), humerus (15 weeks), and femur (16 weeks), fetal hydrops, porencephalic cyst, omphalocele, and foreshortened ribs and limbs. Amniocentesis revealed 46,XY/46,XY,inv(17)(q12q23). The fetus had macrocephaly, subcortical spheric cysts, micrognathia, low set and malformed ears, cleft palate, a small cystic hygroma, pulmonary hypoplasia, omphalocele, short small bowel and bilateral postaxial polydactyly of the hands. Radiographs revealed short ribs, short tubular bones, bowed radius and ulnae, anterior bowing of tibia, and nonosseous postaxial polydactyly. Histopathologic studies of the skeletal system demonstrated disorganized physseal growth zone, irregular vascular penetration of the cartilage at the metaphyseal border, and prominent zone of hypertrophy due to closely arranged large chondrocytic lacunae. Chromosomes from skin fibroblast culture confirmed the mosaic paracentric inversion of chromosome 17q. Chromosomes of both parents are normal.

About 10 cases of Beemer-Langer type SR(P)S have been reported in the literature. Clinical, radiographic and histologic findings of this patient are characteristic of SR(P)S. A de novo paracentric inversion of chromosome 17(q12q25) was reported in a case of campomelic dysplasia (Maria et al, 1991). However, a de novo paracentric inversion of chromosome 17q [46,XY/46,XY,inv(17)(q12q23) (52:8)] observed in our patient has never been reported in Beemer-Langer type SR(P)S. Disruption of two structural genes: Hox-2 and COL1A1, which have been mapped to 17q21-q22 and 17q21.3-q22, respectively (Rabin et al., 1985, Retief et al., 1985), may lead to variable phenotypes which include lethal skeletal dysplasias such as Beemer-Langer SR(P)S and campomelic dysplasia.
ATELOSTEogenesis - BOOMERANG DYSPLASIA (ATG-BD) AND CNS ABNORMALITIES
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The scope of the phenotype and nosology of ATG is evolving with new observations. Now, BD and ATG are considered to be the same. Early investigations stressed the nosologic importance of giant multinucleated chondrocytes (Rimoin et al. 1980), but it has been shown that this feature is inconstant in ATG-BD and can be seen in other chondrodysplasias. (Yang et al. 1983) Similar but distinct dwarfsisms called atelosteogenesis type II and type III have been proposed to account for clinical observations with features of ATG-BG and additional defects.

The characteristic abnormalities of ATG-BD were noted in six patients investigated by Maroteaux (1982) who underscored the importance of micromelia with incurved legs, incomplete ossification of vertebral bodies with coronal cleft of lumbar and hypoplasia of upper thoracic vertebra, hypoplasia and boomerang-like shape of the humerus or tibia and calcification of distal phalanges. We report a black male infant assessed by fetal ultrasonography at 36 weeks gestation because of hydramnios. After delivery, the infant lived 57 days and was noted to have severe rhizomelic micromelia, nasal and midface hypoplasia, cleft palate, absent elbow joints and severe club feet. Radiologic studies showed unossified vertebrae from T6 to T9, a single ossified boomerang-like long bone between the acromion and wrist, short tapered femora, short bowed tibias, absent fibulae (including at necropsy), calcified distal phalanges and irregularly ossified tarsal and metatarsal bones. Postmortem examination showed hypoplasia of cerebral frontal lobes, abnormally developed temporal lobe gyri, asymmetry of cerebellar hemispheres, and a midline posterior cyst-like structure between the cerebellar hemispheres. Histologic examination of long bones showed islands of hypocellular cartilage.

Winship et al. (1990) reported a black infant with ATG-BD, detected, as in our case, because of hydramnios. The infant had a wide defect in the frontoethmoid region and a frontol encephalocele. Chervenak et al. (1986) reported an infant with ATG-BD and severe ocular hypertelorism, malformed ethmoid, frontol cephalocele, bifid tongue and a malformed anterior brain. Kozlowski et al. (1985) described an infant with ATG-BD, an omphalocele and a defect of frontal bones which were replaced by a membrane. Other malformations were also noted in some patients with ATG-BD. The genetic basis of ATG-BD remains uncertain. The presence of CNS and other malformations suggests that perhaps the effects of this disorder, most likely of the mesoderm, may extend beyond the skeletal system.
NEONATAL RADIOLOGICAL CHANGES OF FRONTOMETAPHYSEAL DYSPLASIA (FMD)

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The purpose of this report is to present a case of FMD with distinct skeletal changes at the neonatal age.

A Japanese boy born to healthy parents was referred to us at the age of 8 days because of dysmorphic features, consisting of arachnodactyly, multiple joint contractures, winging scapulae and abnormal facies. The facial abnormalities include hypertelorism, downward slanting palpebral fissures and small pointed chin. The bone survey showed elongated and undermodeled short tubular bones, metaphyseal flaring of long bones, twisted ribs, hooked clavicles, increased interpediculate distance of thoracolumbar spine and flared iliac wings. There was premature ossification of proximal femoral and distal tibial epiphyses, while the carpal bones were not ossified. The epiphyseal ossifications of knees were unusually large in size. The ultrasonography showed cystic dysplastic change of right kidney which turned out later caused by ectopic ureter entering into the seminal vesicle on MRI.

The specific diagnosis of FMD could not be made at this time. The successive bone surveys revealed, however, gradual development of undermodeling and bowing of long bones, and the prominence of supraorbital ridges became manifest at the age of 4 years, at which time the definitive diagnosis was established. This is the first report of fully delineated bony changes in FMD at the neonatal age which is quite distinct and can allow us the early diagnosis.
MICROCEPHALIC OSTEODYSPLOASTIC PRIMORDIAL DWARFISM TYPE II (MOPD II) IN A BOY WITH CONSANGUINOUS PARENTS
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MOPD II has previously been described in 9 patients. The main features are a microcephalic "bird-headed" craniofacial appearance, primordial and postnatal dwarfism which in the first year of life is disproportionate with relatively short extremities. X-rays show brachymesophalanx, brachymetacarpal I, pseudoepiphyses of the tubular bones of the hands and characteristic radiological changes of the femoral metaphyses, narrow pelvis and coxa vara.

We present a boy born to healthy, consanguineous turkish parents. Weighth, length and FOC at birth were below P3 for turkish boys. The small head with a prominent nose and mild micrognathia was proportionate in relation to the trunk but the extremities were disproportionately short. Growth retardation was aggravated by severe nutritional problems and recurrent infections due to transient IgG2 subclass deficiency - factors which initially disturbed the diagnostic picture. In the third year of life the disproportion of the extremities disappeared, but cranial growth practically stopped. The radiological findings comprised a proximal pseudoepiphysis of the 2nd metacarpal bone, brachymetacarpal I and brachymesophalanx V. The femoral metaphyses were cupped and the femoral necks were in varus position. At 4 1/2 years motor and mental development appear normal for age but the body measurements remain below P3.

On this basis the diagnosis of MOPD II was made. Parental consanguinity support the suspicion of autosomal recessive inheritance. In spite of normal growth hormone excretion treatment with growth hormone is now tested in this patient.
SCHMID METAPHYSEAL CHONDRODYSPLASIA IS CAUSED BY A MUTATION IN THE GENE FOR TYPE X COLLAGEN

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The expression of the extracellular matrix protein, type X collagen, is restricted to hypertrophic chondrocytes in regions undergoing endochondral ossification. To determine the precise role of type X collagen in this process we have examined the COL10A1 gene in several forms of human osteochondrodysplasia. We identified a 13 bp deletion in all affected members from a large family with Schmid metaphyseal chondrodysplasia. The LOD score for this mutation with the Schmid phenotype was 18.2 at θ = 0. The mutation results in a frameshift which alters the carboxyl-terminal 60 amino acid residues in the polypeptide. The likely effect of this mutation is to prevent association of the mutant polypeptide chain during trimer formation, thereby reducing the amount of normal type X collagen. Based upon the clinical feature of Schmid metaphyseal chondrodysplasia and upon the phenotype of two dominant negative type X collagen mutations in transgenic mice, we suggest that one role of type X collagen is to structurally stabilize the hypertrophic zone of growth plates. Human type X collagen gene mutations which severely reduce the production of normal type X collagen or result in matrix deposition of an abnormal protein, would be predicted to cause more severe forms of osteochondrodysplasia.
A NEW SKELETAL DYSPLASIA AND ASSOCIATED MULTIPLE ORGAN SYSTEM ABNORMALITIES

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In 1990, Saul and Wilson reported on two males with a previously undescribed skeletal dysplasia. Associated features included an unusual facial phenotype, clubfoot deformities, brachydactyly, and variable intelligence. We describe a female with similar clinical and radiographic abnormalities.

At term, the patient was small for dates. She had facial anomalies and clubfoot deformities. A syrinx was found at age 2, and cataracts developed at age 3. Intelligence was normal. She developed short stature, microcephaly and brachydactyly. At age 4, height was 82 cm and OFC 45 cm. Facialy, she had a high forehead, beaked nose, small midface, bifid uvula and micrognathia.

Significant radiographic findings included: overtubulation of the long bones of the extremities; platyspondyly, with hypoplasia of L-1 and odontoid process; short metacarpals, metatarsals and phalanges; accessory ossification centers of metacarpals and metatarsals; and coning and sclerosis of several epiphyses of distal phalanges.

Similar clinical and radiographic manifestations support the notion that the three cases have evidence of a new skeletal dysplasia associated with variable involvement of other organ systems. Absence of similar features in our patient's four siblings, and three sibs of a previous case, mitigates against autosomal recessive transmission, and suggests a de novo autosomal dominant mutation as its origin. Although rare, characterization of additional cases should enable delineation of the full spectrum of this multisystem disorder and development of appropriate management strategies.
PRESUMED AUTOSOMAL DOMINANT FETAL AKINESIA SEQUENCE: FINDINGS IN SIBS AND HALF SIBS FROM THE SAME MOTHER

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Fetal akinesia sequence in sibs may not be unusual, but fetal akinesia in half sibs, one a male infant, might be unique - seemingly representing autosomal dominant inheritance with variable expressivity. We have encountered four offsprings from the sequential mating of one mother with three different mates, unrelated to her or to each other. The mother begot from the first father one lethal female infant; from the second father three lethal female infants, one of whom unknown except by history, and two normal female children; and from the third father one lethal male infant. Prenatal ultrasonography, postnatal radiography and autopsies were obtained on four of five lethal offspring. One infant with a multiple lethal pterygium phenotype had hydrops fetalis with pterygia of multiple large joints and pulmonary hypoplasia. Another with a Pena-Shokeir phenotype had arthrogryposis, severe pulmonary hypoplasia, and mild cerebral gliosis. A third showed pulmonary hypoplasia, micrognathia, hip dislocations and clubbed feet. The fourth had severe hydrops fetalis with pulmonary hypoplasia, but no mention of joint contractures. The features in these infants may reflect decreased in utero fetal movement in a variable single heritable variable disorder.
A NEW SYNDROME OF MULLERIAN DYSGENESIS, FACIAL HYPOPLASIA, BILATERAL FOREARM DEFORMITY, BRACHYDACTYLY, SPINAL STENOSIS AND SCOLIOSIS.

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J. P. MASSEL (PAEDIATRIC RADIOLOGIST, THE ROYAL CHILDREN’S HOSPITAL, BRISBANE, AUSTRALIA)

Developmental abnormalities in a 2½ year old girl with bilateral conductive deafness are described. Facial dysmorphic features include prominent supraorbital ridges, facial hypoplasia, facial asymmetry, downward slanting palpebral fissures, high prominent nasal bridge with bifid nasal tip and a small lower jaw, and hypoplastic ear lobules with bilaterally narrow and oblique external auditory canals. Clinical and radiological examination has revealed various skeletal abnormalities including hypoplastic facial bones, hypoplastic clavicles, narrow and anteriorly sloping shoulders, bowing of both bones of forearms, brachydactyly due to short metacarpals and hypoplastic terminal phalanges, thoracolumbar kyphoscoliosis, narrow transverse measurements of most vertebrae with prominent coccyx, spinal canal narrowing, hypoplasia of the lower ilia, medially bowed femora, tibiae and fibulae and brachysyndactyly of the second, third and fourth toes bilaterally. Gynaecological evaluation revealed abnormalities of the Mullerian duct structures and the urogenital sinus, a vestigial uterus, posteriorly placed small but patent vagina and a septum at the vaginal introitus. The constellation of the facial dysmorphic features and unusual skeletal abnormalities associated with maldevelopment of the uterus and vagina are not consistent with a previously described recognizable syndrome or association, possibly a new syndrome within the ‘community of syndromes’ involving anomalies of the Mullerian duct structures, limbs, spine and ears.
TWO SIBLINGS WITH GALACTOSIALIDOSIS

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Y. Ogihara, M. Yamazaki (Department of Orthopaedic Surgery, Mie University Hospital, Tsu city, Japan)
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Two siblings with Galactosialidosis, which is a very rare condition, are reported. They were 11- and 6-years-old males, who were the first and second born of healthy parents. The family history revealed no consanguinity or other congenital anomalies. Physical examinations of the two patients revealed similar findings which were short stature (elder brother: 115cm, 17kg, younger brother: 92cm, 12kg), peculiar face resembling Gargoyleism, lumbar kyphosis, contractures of bilateral hip and knee joints, and mental retardation. Roentgenological findings of the two patients were also similar and revealed bilateral dislocation of the hip joints and skeletal changes (spine: hypoplasia of the lumbar bodies and a localized kyphosis, pelvis and femur: hypoplasia of the bodies of the Ilia, small and poorly ossified capital femoral epiphysis and coxa valga, hand: delay of bone age and slightly increased width of metacarpal bones). In the elder brother, biochemical examinations showed combined decrease of activity of lysozomal β-galactosidase and N-acetyl-neuraminidase.
A CLINICAL AND RADIOLOGICAL STUDY OF SKELETAL DYSPLASIAS

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A hospital based study of clinical and radiological aspects of skeletal dysplasia was carried out in three teaching hospitals in Davangere (a south Indian town), for a period of 2 years. We studied 180 cases of inherited disorders of skeleton out of which 113 cases were skeletal dysplasias which were grouped according to International classification of osteochondrodysplasias (second revision 1991). 80% of cases belonged to pediatric age group. In 7 cases antenatal diagnosis was made using ultrasound examination. Osteogenesis imperfecta (13 cases) was the one having maximum incidence. Other disorders having high incidence included, osteopetrosis (9), mucopolysaccharidosis (8), Thanatophoric dysplasia (5), Metaphyseal dysplasia (5) Campomelic dysplasia (6) Fibrous dysplasia (5), Achondroplasia (4), Engelmann disease (4), VATER Association (7), Treacher Collins Syndrome (5), Marfan Syndrome (5), Beals Syndrome (4) and Weill Marchesani Syndrome (4). Several classical cases of rare disorders like Pyle disease, Pycnodysostosis and Engelmann disease were identified.

Though not a population based study, the identification of a large number of cases with inherited skeletal disorders in a relatively short period, gives an idea regarding the prevalence of skeletal disorders in the community. This high incidence may be due to high degree of consanguinity prevalent in this part of the country.
WAS VESALIUS A DWARF?
A SPECULATIVE PAPER

M.H. Hast,¹ D.H. Garrison,² A.K. Poznanski³ (¹ Northwestern University and Northwestern Memorial Hospital, ² Northwestern University, ³ Northwestern University and The Children's Memorial Hospital)

This paper will discuss the possibility that Andreas Vesalius may have suffered from a short-limbed dwarfism. The evidence for some form of bone dysplasia is based primarily on the portrait of Vesalius used as the frontispiece of his anatomical treatise De humani corporis fabrica (1543, 1555). Examination of the portrait reveals a young man with a normal-sized head but large in proportion to his short stature (compared to the cadaver he is dissecting); both his arm and forearm are short, his fingers are long, and his abdomen appears prominent. This portrait and other anatomical drawings in the Fabrica have been attributed to the artist Joannes Stephanus van Calcar. The authors will discuss this portrait and another of Vesalius by van Calcar, together with other anatomical drawings of the Renaissance. The authors will ask whether the frontispiece portrait is a true representation of Vesalius or the work of an unskilled artist, and what type of dysplasia, if any, accounts for the disproportions shown.
Was Vesalius a Dwarf?

Malcolm H. Hast
Daniel H. Garrison
Andrew K. Poznanski
Northwestern University

ANDREAE VESALII.

Bone Dysplasia Society
June 18-19, 1993

Above: Portrait of Vesalius attributed to Jan van Calcar, used as frontispiece of the 1543 and 1555 editions of the Fabrica and the Epistle on the China Root (1546)

A Short Vesalian Reading List


DEFORMED DWARFS OF VIENNA

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The Museum of Pathological Anatomy, Vienna, houses a remarkable collection of osseous material, some of which is of considerable antiquity. Diagnostic appraisal has been undertaken in order to recognize genetic conditions amongst these specimens, and a variety of common and rare heritable disorders have been identified. In some instances radiographic investigations have been necessary for diagnostic confirmation. Well defined dwarfing disorders which are represented include achondroplasia, thanatophoric dysplasia and osteogenesis imperfecta type II.

Other skeletal conditions in which stature is stunted, include cleidocranial dysostosis, diaphyseal aclasia and various forms of rickets.

The Viennese collection is an important academic resource which warrants the attention of all colleagues who share an interest in genetic bone dysplasias.
ANCIENT SKELETONS OF AN ACHONDROPLASTIC MOTHER AND INFANT

A.K. Poznanski (The Children's Memorial Hospital, Northwestern University, Chicago, IL 60614), J. Buikstra, S. Burgess (University of Chicago, Chicago, 60637)

During an archaeologic study in southern Illinois two skeletons were found at the same site which had the characteristic appearance of achondroplasia. It is likely that the mother died during childbirth.
LESS WELL KNOWN ASPECTS OF CLASSIC OSTEOPETROSIS

C. B. Graham (University of Washington School of Medicine and Children's Hospital & Medical Center, Seattle, Washington)

It will be shown that the mother of Albers-Schonberg's original case also had this so-called autosomal recessive condition. Relatively less bone sclerosis in utero indicates a maternal or fetal protective influence. The osteosclerotic process shows evidence of partial remissions and exacerbations throughout post-birth development, suggesting the presence of circulating humoral factor. A very unusual asymmetrical related dysplasia will be presented for discussion.

Reference:

UNKNOWN CASE PRESENTATIONS

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ABSTRACT

UNKNOWN DWARF

HARRIS, V., YOUNG, S., WILKS, A., AND HARRIS, K. COOK COUNTY CHILDRENS HOSPITAL, CHICAGO, IL.

THE INFANT WAS AN ARABIC FEMALE, 40 WEEKS GESTATIONAL AGE, BORN TO A 27 YEAR OLD G3P2001 MOTHER VIA CESARIAN SECTION. THE MOTHER HAS A HISTORY OF RHEUMATIC FEVER AT AGE 19. SHE HAD AN INFANT PREVIOUSLY WITH SIMILAR CONGENITAL ANOMALIES, WHO DIED AT BIRTH. NO AUTOPSY WAS PERFORMED. HER FIRST CHILD IS NORMAL. SHE USED NO MEDICATIONS DURING PREGNANCY. THE INFANT WAS NOTED TO HAVE SHORT LIMBS, A NARROW CHEST WALL, WAS INTUBATED FOR SEVERE RESPIRATORY DISTRESS, DID NOT RESPOND TO RESUSCITATION AND DIED 6 HOURS AFTER BIRTH.

AUTOPSY: WEIGHT 2750 GRAMS, LENGTH 38 CMS. HEAD CIRCUMFERENCE 30 CMS, ABDOMEN CIR. 36 CMS., CROWN RUMP 35 CMS.. RIBS CURVED, NARROW WITH LARGE CARTILAGE ZONES. FEMUR AND TIBIA EXTREMELY SHORT WITH WIDE CARTILAGE ZONES AT BOTH ENDS, AND LITTLE BONE FORMATION. BOTH BONES ARE AT 45 DEGREE ANGLES AT THEIR MID-POINTS. PULMONARY HYPOPLASIA PRESENT. BRAIN SHOWED POLYMICROGYRIA, BUT NORMAL SIZE, WITH NO OTHER ABNORMALITIES. ABNORMAL FACIES WITH DEPRESSED NASAL TIP, SEVERE MICROMELIA, NARROW THORAX, SHORT NECK AND DISTENDED ABDOMEN.

RADIOLOGY: HIGH "S" SHAPED CLAVICLES, SHORT DEFORMED RIBS, SCAPULA IRREGULAR, HUMERUS SHORT WITH WIDE METAPHYSIS, FLATTENED VERTEBRAE, FEMUR, TIBIA AND FIBULA WIDE, SHORT, BOWED WITH CONCAVE ENDS.
SEVERE MESOMELIC DWARFISM, BIFID SPINE AND CLEFT PALATE

F.A. Beemer (Clinical Genetics Center Utrecht) and P.P.G. Kramer (Dept. of Radiodiagnosis University Children's Hospital Het Wilhelmina Kinderziekenhuis, Utrecht, The Netherlands).

The male proband was born after an uneventful gestation of 39 weeks as the 5th child of healthy, consanguineous parents. The other children were healthy. Besides, the mother had had one stillborn at 6 months gestation; this child was reported to have no visible abnormalities. The proband's birth weight was 2600 g, length 44 cm, OFC unknown. Clinically there was a rhizomelic micromelia. There were dysmorphic facial features: bulging eyes, upturned nose and a short neck. He also had a cleft palate. Hands and feet were small.

On radiography, mesomelic shortening of the limbs was apparent. There was a bifid spine C7-D1 and L4-S2 as well as a scoliosis. The iliac wings of the pelvis were round with horizontal acetabular roofs. On the hands, short tubular bones were present.

At the age of 7 years his somatic growth is severely retarded: length 86 cm (23 cm minus P3), weight P75, OFC 49.5 cm (-1SD). His dwarfism is of the short-limb type. His psychomotor development is slightly retarded. The dysmorphic facial features were similar but more expressed than at birth. He suffered from recurrent upper respiratory tract infections. He also had a hypertension from unknown origin. Seven years ago his data were sent to drs. Spranger, Maroteaux and Langer. However, no definite diagnosis could be made.
L. M. Drummond-Borg, M.D., F.A.A.P. (Genetic Screening and Counseling Service, 3600 E. McKinney, Denton, TX 76201)

J.U. is a 7-year-old boy who was born at 35 weeks gestation with Apgars of 2 at 1 and 7 at 5. Weight: 3189 g. Length: 50 cm. OFC: 35 cm. He had severe RDS, low-set ears, short humeri, large anterior fontanelle, cloudy corneae, umbilical hernia, and edema.

Karyotype was 46,XY. Lysosomal enzymes, thyroid function studies, urine sialic acid, mucopolysaccharides, and metabolic screen were normal.

His skeletal survey at 5½ years showed a bone age of 1½ years. The skull x-rays showed multiple wormian bones with widening and delayed fusion of the fontanelles, extreme sclerosis and thickening, and a small J-shaped sella. The acetabulae were horizontal.

At the age of 7 years, J.U. is floppy, markedly delayed in development, and the size of a 3-year-old, with a head circumference on the 90th percentile for a 7-year-old. His appearance has not changed much since birth. He has simple ears, hypertelorism, large tongue, coarse face, narrow chest, umbilical hernia, trident hands which are in proportion to his height but his arms and legs look short. There is no family history.
UNKNOWN CASE

D.S. Newcombe (Bedford VA Hospital, Bedford, MA), A.K. Poznanski (The Children's Memorial Hospital, Chicago, IL)

This lady is on the short side, about 5 feet 2 inches, and had a hip replacement at age 36 for osteoarthritis. She is now having pain in her right hip. She is relatively asymptomatic with respect to her knees at this time.

The patient's family history of premature arthritis is entirely negative so she probably represents a recessive form of the disease. I suspect films of the hand and feet would be the best screen for affected children.
B. Pontz\textsuperscript{1}, P. Freisinger\textsuperscript{1}, A. Nerlich\textsuperscript{2}, H. Stöß\textsuperscript{3}, D. Färber\textsuperscript{1}, P. Maroteaux\textsuperscript{4}

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A new type of a severe micromelic osteochondrodysplasia (OCD) with platyspondyly and large metaphyses

Our patient, the third child of healthy, unrelated parents with a unremarkable family history presented at birth with severe disproportionate dwarfism, short limbs, a short bell-shaped thorax, macrocephaly, a dysmorphic face and cleft palate. No malformation of the inner organs and CNS were detected by ultrasound. She required intermittent artificial respiration from birth and died at seven months. Radiographs showed tubular bones with short diaphyses and wide, convex, irregular metaphyses. The irregular shaped, vertebral bodies were remarkably flat. The iliac bones are small, squared and dysplastic in their inferior parts. There is some delay in ossification of the vertebral bodies and the pelvic bones. Chest X-ray showed a short, proximally narrow thorax with horizontally oriented ribs. Radiographs of the skull revealed midface hypoplasia. Clinical data will be completed by histomorphological analysis. This case shares features with some OCDS like Kniest Dysplasia, Dyssegmental Dysplasia and variants of the perinatally lethal, spondyloepiphyseal dysplasias but is clearly distinct from these entities by the combination of the abnormalities.
UNUSUAL LETHAL BONE DYSPLASIA WITH BOWED LEGS.

H. Stoess¹, B. Künn¹, J. Spranger²

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In an 18-year-old pregnant woman, intrauterine foetal death occurred in the calculated 31st week of the pregnancy. On inspection of the highly macerated foetus, retardation of growth was noted. The length and weight of the foetus were compatible with the 24th week of pregnancy. Although the length of the trunk was almost normal, the limbs were greatly shortened and bowed. X-ray examination of the long tubular bones, in particular of the lower limbs, revealed an almost right-angled campomelic bowing. All the tubular bones showed variable degrees of bowing. The ends of the ribs sometimes showed paddle-like enlargement. The changes were similar to those described by STEVENSON in 1982, although in our case there were no prenatal fractures and no ankyloglossia. As far as we know, no similar cases have been reported in the literature.

Reference:
Stevenson, R.E.: Campomelia, Prenatal Fractures and Ankyloglossia Superior.
A NEW SPONDYLOEPIPHYSEAL DYSPLASIA SYNDROME?

J.J. Hoo, M.B. Sheinkop (Departments of Pediatrics and Orthopedic Surgery, Rush-Presbyterian-St. Luke's Medical Center, Chicago, IL 60612)

A 2 1/2 year old Caucasian boy was affected with "knocked knees", which was first noted at 1 year of age, but became more prominent a year later. His pre-, peri- and postnatal history was unremarkable, but he is suffering from asthma and is allergic to various substances. His psychomotor development is normal. The family history is also unremarkable, there is no consanguinity.

He was chubby and stocky, with height and head circumference at 50th percentile, but weight at 95th percentile. His intelligence and developmental milestones were normal. Bilateral genu valga, bilateral subtle epicanthal folds, long philtrum, bilateral receding second toes overlapping the third toes, and stocky fingers were apparent at physical examination. There was no organomegaly.

Skeletal survey revealed flattening of vertebral bodies, relatively small ilia with flattened acetabular roof, coxa valga, small epiphyses of the femur and proximal tibia, genu valga, as well as short and broad metatarsals, metacarpals and phalanges.

The knocked knees prompted enzyme studies for Morquio disease, but both beta-galactosidase and N-acetyl galactosamine 6 sulphate sulphatase were normal, as well as serum Ca, P, alkaline phosphatase, vitamin D, amino acids, and other chemistry. Urine organic acids and glycosaminoglycan were also normal.
UNKOWN CASE

P.S. Karnes (Mayo Clinic, Rochester, Minnesota)

A 3-year-old girl who is referred to genetics for evaluation of advanced bone age and to rule out skeletal dysplasia. The maternal grandfather, age 52, is 6'1" tall. He had hypertension and gout. The maternal grandmother, age 48 or 49, is 5'2" tall and healthy. The mother, age 24 is 5'6" tall and healthy. Maternal uncle 5'6" tall and healthy. Maternal uncle is 6'1" tall. Maternal uncle 6 fee tall and healthy. Maternal uncle is 5'10" or 5'11" tall and healthy. The father is 5'7" tall. Parental uncle is 6 feet tall. Parental uncle is 5'11" tall. Parental uncle is 5'5" tall and is healthy. Sister (III.3) Kelsey Stovall, age 5 months, is healthy.

CLINICAL FINDINGS: During pregnancy mother was taking no medications or contraceptives at the time of conception. Four of five days after her due date she went into spontaneous labor. Brittany had a birth weight of 7 lbs 8.5 oz. During the first half year of her life Brittany's weight gain was normal despite frequent regurgitations of her formula.

At age 11 months bilateral hip dysplasia was diagnosed. It was not responsive to closed reduction, so open reduction at age 1 year and 3 months was undertaken which was followed by casting for 3 months. She then had a femoral fracture in November of 1990 which was treated with 8 weeks in a cast. There has been progressive external rotation of that leg since that time. She has not been able to walk unassisted since birth. She crawls army combat style and uses a walker to ambulate. Since November of 1990 Brittany complained on pain in her neck and her head had been tilted to the left for the past year. Her parents have been aware that her spine is curved for about the same length of time but no treatment had been recommended. Brittany complains of bilateral leg and hip pain which is worse at night and causes her to cry. A muscle biopsy showed type II fiber atrophy. Her creatine phosphokinase has been consistently normal. Her karyotype was normal. Urine mucopolysaccharide and oligosaccharides were normal. An EMG was normal. An MRI of the head was probable normal except for showing chronic sinusitis. Brittany's mental development has been normal.

Examination (3 years): Weight 14 kg (50th percentile). Height 91 cm (accuracy questionable due to the contractures, 5-10th percentile). Head circumference 50.5 cm (75th percentile). Inner-canthal distance 3.5 cm (>97th percentile). Interpupillary distance 5.0 cm (70th percentile). Ear length 5.0 cm on the right (25th percentile) and 4.7 cm on the left (10th percentile. Head: There is thick soft blond hair with normal anterior and posterior hairlines and a double parietal hairwhorl to the right midline. There is some frontal bossing and midface flattening. There is a mild brachycephaly and plagiocephaly particularly evident in the face. Extraocular movements are intact. The pupils are small, equal, and reactive to light. She does not have corneal clouding although there is a subtle sense of decreased shininess in looking at the cornea. The nose, philtrum, lips nad face are normal. Dentition is significant for deficiency of the median portion of the central upper incisors. The first lower incisors are quite small.
relative to the second lower incisors. The palate is normal in shape and there are no thickened palatine ridges. The tongue is normal. She is hyperextensible at the wrist, MCP,PIP, and DIP joints of the hands. There is no dysmorphism of the hand. There is a full range of motion at the knees, ankles, and toes with no dysmorphism of the lower extremities. She sits with her head turned slightly to the left and moves her entire trunk in order to see things to the right. When standing she is unable to fully extend the hips.

**Investigation:** Muscle biopsy (607090 Washington University): “Type 2 fiber smallness. This change is nonspecific. It may be a congenital abnormality or may be secondary to CNS changes with disuse.” Electroencephalogram (1-6-92 Phelp’s County Regional Medical Center) "Abnormal EEG due to intermittent rhythmic discharges over the right temporal region. The rhythmic paroxysmal activity noted in the right temporal region of the study could be consistent with a clinical seizure disorder. Clinical correlation is recommended."

**Mayo Clinic Investigations:** Hemoglobin 12.0 gm/dL. MCV 86.1, leukocytes 6,800 with 30% neutrophils. 60% lymphocytes, 5% monocytes, 4% eosinophils, 1% basophils. Platelet count 392,000.


**Outside investigations:** Medical records have been received from Washington University School of Medicine. It is noted that very long chain fatty acids and phytic acid results from John Hoskins in Dr. Moser’s lab were normal. Chromosome analysis (8-30-90): Normal, 46, XX. Plasma amino acid (7-05-90): Entirely normal. Oligosaccharides (5-22-92): Normal. Urine inborn error screen (5-19-92): No abnormalities detected. Thyroxine binding capacity (5-19-92): 15.1 g/Dl. This suggests that the slightly low serum thyroxine is due to low binding capacity. White blood cell B-galactosidase (5-19-92): 2.96 U/10^10 cells (normal). Serum T3 (5-19-92): 172 ng/dL (normal). Serum N-acetyl glucosaminidase: 0.32 U/L (normal). 7-30-92 Tissue mucopolysaccharide evaluation (7-29-92): The mucopolysaccharide screen performed on this patient’s fibroblasts showed normal sulfate turnover. This result out mucopolysaccharidoses I, II, III, VI, and VII.
UNKNOWN CASE #1

P. Beighton (University of Cape Town, South Africa)

A female aged 31 years, living in a remote rural area, presented in Cape Town with short trunk dwarfism, a long-standing mid-thoracic gibbus and a barrel chest. Her general health was good and, apart from mild genu valgus, pes planus and a Caesarian section scar, there were no additional significant clinical abnormalities. Chest radiographs revealed a mass at the right pulmonary hilum and a tentative diagnosis of tuberculosis of the lungs and spine was entertained. Skeletal radiographs confirmed the gibbus and showed mild biconcave platyspondyly and marked shortening of the femoral necks. The skeleton was otherwise essentially normal.

The diagnostic situation was resolved when the patient's son, aged 6 years, was also found to have short trunked dwarfism with a mid-thoracic gibbus. He was otherwise healthy and clinically normal. Radiographs revealed marked biconcave platyspondyly, which was especially severe in the cervical region. The upper femoral metaphyses showed patchy lucency and sclerosis and the femoral heads were mildly dysplastic. Bone age, in terms of carpal development, was delayed.

A diagnosis of autosomal dominant brachyolmia was established.
UNKNOWN CASE #2

P. Beighton (University of Cape Town, South Africa)

SW, a male born in 1899, died of pneumonia in a children's hospital in 1901. The child was dwarfed, with bowing of the femora and bones of the forearms. The maxillae showed gross expansion and similar changes were present to a lesser extent in the mandibles. The skeleton was preserved in the museum of anatomical pathology in Vienna where a diagnosis of "rickety dwarfism with leontiasis osseum" had been recorded.

Diagnosis: Osteoectasia (Hyperphosphatasia)?
UNKNOWN CASE #1

R.S. Lachman (Harbor-UCLA Medical Center, Torrance, California), D. Rimoin (Cedars Sinai Medical Center, Los Angeles, California)

Presented in 1991 at the age of 6 years and 9 months with short limbs, dislocated hips and brachydactyly. The intellect was normal, as were other body systems and the family history was negative. At that time, the clinical and radiographic features were regarded as being consistent with pseudoachondroplasia.

He was examined again in 1992, at the age of 12 years, and found to have shortened stature (height, 104 cm, <3rd centile) and limb shortening. Joint hypermobility had resulted in pes planus, valgus ankles and a mild scoliosis of the spine. In addition, by that stage, asymmetrical contracture of the upper thorax. This latter feature led to a subsequent diagnosis of enphysema thoracis diastrophic dysplasia.

Radiographic studies in 1992 showed that the metaphyses were now expanded with increased angles and patch of lunulae and epiphyses, which were suggestive of enchondromatosis. The diaphyses of the tubular bones were short, especially in the carpal bones. Mild platypody at was present and bicipitally had developed in the lower thoracic and upper lumbar vertebrae. The upper portion of the chest was narrow and the ribs were horizontal and wide.

Diagnosis: Enphysema thoracis diastrophicus (D)
UNKNOWN CASE

P. Beighton, P. Zack (University of Cape Town, South Africa)

A boy living in a rural area of the Cape Province, Republic of South Africa presented in 1981 at the age of two and a half years with short limbed dwarfism and brachydactyly. His intellect was normal, as were other body systems and the family history was negative. At that time the clinical and radiographic features were regarded as being consistent with pseudoachondroplasia.

He was examined again in 1992, at the age of 13 years, and found to have stunted stature (height 104 cm, < 3rd centile) and limb shortening. Joint hypermobility had resulted in pes planus, valgus ankles and a mild thoracolumbar scoliosis. In addition, he had marked asymmetrical constriction of the upper thorax. This latter feature led to a tentative diagnosis of asphyxiating thoracic dysplasia.

Radiographs obtained in 1992 showed that the metaphyses were now expanded with numerous streaks and patches of lucency and sclerosis, which were suggestive of enchondromatosis. The diaphyses of the tubular bones were short, especially in the extremities. Mild platyspondyly had persisted and biconcavity had developed in the lower thoracic and upper lumbar vertebrae. The upper portion of the chest was narrow and the ribs were horizontal and wide.

Diagnosis: Spondyloenchondromatosis (?)
UNKNOWN SYNDROME

M. Le Merrer, P. Maroteaux (Hopital des Enfants-Malades, Paris, France)

The authors described two sibs with metaphysial dysplasia, deafness and retinal lesions. The disease was detected when one of the boys was 5 years old at the time of a radial fracture.

The two boys had a profound deafness and were known to have some pigmented retinal lesions without visual defect. They have also blue sclerae and one of them had a large decreased pigmental patch on the trunk and on the right shoulder. The nails were hypoplastic. The height of the two children were normal for chronological age.

On the x-rays metaphysial changes of the wrist and of the ankle were detected: irregularities of the distal metaphysial region of the two bones with a netting aspect, but without flaring. On the knee and on the hand the lesions were more moderated. The calcium levels, the alkaline phosphatases and specially phospho-ethanolamine were normal, eliminating a slight form of hypophosphatasia.

After a careful search in the literature, we have been unable to find a known etiology of this association, which might be autosomal recessive or X-linked.
UNKNOWN CASE #2

R.S. Lachman (Harbor-UCLA Medical Center, Torrance, California), D. Rimoin (Cedars Sinai Medical Center, Los Angeles, California)
UNKNOWN CASE

H. Taybi (University of California, San Francisco, California)
OTHER CASE PRESENTATIONS
June 19, 1993