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Skeletal Dysplasias in the Newborn: Diagnostic Evaluation and Developmental Genetics

Daniel T. Swarr, MD,* V. Reid Sutton, MD†

Abstract

Many of the genetic disorders of skeletal development lead to significant morbidity and mortality in utero or in the early neonatal period. Due to the large number and heterogeneous nature of these disorders, their diagnosis and management can be overwhelming. A basic knowledge of skeletal development and a structured, comprehensive approach to the history, physical examination, and interpretation of radiographic studies are crucial. Understanding the power and limitations of prenatal diagnostic technology and genetic testing is essential for accurate counseling and judicious use of resources. Finally, familiarity with individual disorders and online resources aids the neonatologist in coordinating the complex, multidisciplinary care that these infants demand in the neonatal intensive care unit (NICU) and after hospital discharge.

Objectives After completing this article, readers should be able to:

1. Define the terms “dysplasia” and “dysotosis” and describe common skeletal abnormalities using accepted terminology.
2. List key elements of the history and physical examination of a neonate in whom a disorder of skeletal development is suspected, describe how to interpret a skeletal survey, and collectively use these data to search major atlases and databases.
3. List the most common disorders of skeletal development presenting in the newborn period, characteristic features of each disorder, and the molecular basis for each condition, if known.
4. Discuss the initial treatment of a neonate presenting with a suspected disorder of skeletal development.

Introduction

Genetic disorders of skeletal development are a large, extremely heterogeneous group of conditions that may present anytime from the prenatal period to adulthood. The estimated incidence of disorders of skeletal development manifesting in the neonatal period is 15.7 per 100,000 births. Long-term prognosis ranges from inevitable death shortly after birth to survival into adulthood with normal intellectual development. In the neonatal period, respiratory compromise is the leading cause of morbidity and mortality.

Skeletal dysplasias are developmental disorders of chondro-osseous tissues or an “abnormal organization of cells into tissue and its morphologic result.” (1) These disorders are the result of an insult that occurs after organogenesis but persists throughout later stages of development into postnatal life. Dysplasias are referred to as primary if they result from mutations in genes expressed in chondro-osseous tissues and secondary if they result from extraosseous factors that affect development of bone. Dysplasias continue to affect the skeleton through late pre- and postnatal life, lead-
According to short stature, differing clinical characteristics with age, and in some cases, an increased risk of primary malignancies of chondro-osseous tissues. In contrast, dysostoses are “malformations of single bones, alone or in combination,” as a result of an insult during organogenesis (1). They are typically the result of a discrete insult during organogenesis. As such, they are static lesions without risk of progression or malignant degeneration and usually are not associated with short stature. Key definitions important in the diagnosis of these disorders are summarized in Table 1.

To date, 372 disorders have been described and classified into 37 groups. (2) As the number of disorders of skeletal development has increased and understanding of their molecular causes has grown, this classification system has evolved into a complex amalgam of clinical, radiographic, biochemical, and molecular features. Some classification groups are based purely on molecular cause (eg, FGFR3 group, type II collagen group), others are based on radiologic findings (eg, metaphyseal dysplasias group, increased bone density group), and yet others are based on a combination of clinical and radiographic features (eg, mesomelic and rhizomelic dysplasias, bent bone dysplasias group).

This bewildering array of disorders and terminology can make the approach to a newborn who has a suspected disorder of skeletal development overwhelming for even the most experienced clinician. In this article, we review basic aspects of skeletal development, discuss how to approach an infant who has a suspected skeletal dysplasia or dysostosis, summarize common and important disorders of skeletal development presenting in the neonatal period, and present advances in treatment.

Case Presentation

You are called to evaluate respiratory distress and cyanosis in a term infant who was born to a 35-year-old multiparous woman following a cesarean section for failure to progress. The mother received late prenatal care, but her serology results were within normal parameters. In the delivery room, the infant developed mild tachypnea and cyanosis that improved with oxygen administered by nasal cannula. On physical examination, the infant has a weight of 3,830 g (71st percentile), head circumference of 39 cm (97th percentile), and length of 40 cm (−3.7 standard deviations below the mean). Despite a small chest, his lung fields are clear, and cardiac examination yields normal results. The most striking findings on examination are short upper and lower extremities and bilateral club feet. You transfer him to the NICU for further evaluation.

Overview of Skeletal Development

Development of the skeleton begins very early in embryonic life, starting with patterning of the somites during the end of the third week and formation of the limb buds during the fourth week of embryogenesis. Complex molecular pathways mold the somites into the developing axial skeleton, which ultimately consists of the vertebral column, scapula, ribs, and pelvis. Distinct, yet equally sophisticated developmental signals direct the primordial limb buds to form the mature appendicular skeleton. Disruptions in these early patterning events classically result in dysostoses (Table 2).

Patterning of the skeleton is followed during the fifth week of development with the formation of cartilage from mesenchyme or embryonic connective tissue. The skeleton subsequently develops through two primary mechanisms: intramembranous ossification and endochondral ossification. In intramembranous ossification, neural crest-derived mesenchymal stem cells condense and differentiate directly into bone. This process is involved primarily in the formation of the flat bones of the skull and proximal portions of the clavicles. The remain-

Table 1. Key Definitions

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Skeletal dysplasia</td>
<td>&quot;An abnormal organization of cells into [chondro-osseous] tissue(s) and its morphologic result(s)&quot; (1)</td>
</tr>
<tr>
<td>Primary skeletal dysplasia</td>
<td>A skeletal dysplasia due to mutated genes that are expressed in chondro-osseous tissue</td>
</tr>
<tr>
<td>Secondary skeletal dysplasia</td>
<td>A skeletal dysplasia due to abnormalities of extraosseous factors with secondary effects on the skeletal system</td>
</tr>
<tr>
<td>Dysostosis</td>
<td>&quot;Malformations of single bones, alone or in combination,&quot; as a result of an insult during organogenesis (1)</td>
</tr>
<tr>
<td>Disruptions</td>
<td>Secondary malformations of bones as a result of exposure to a noxious agent (such as an infection or toxin) during a limited period during development</td>
</tr>
<tr>
<td>Osteolysis</td>
<td>Postnatal disruption of bone development (includes hereditary and external causes, such as infection, neuropathies, and toxic exposures)</td>
</tr>
</tbody>
</table>
der of the skeleton is formed through endochondral ossification, whereby mesenchymal stem cells initially create a well-organized cartilage structure that subsequently is converted to bone. A number of disorders result from disruption of this normal differentiation process, leading to a phenotype of abnormal skeletal patterning as well as a defect in skeletal growth. Because these disorders combine features of dysotosis and dysplasia, they sometimes are referred to as dysostoplasias. Prototypic examples include campomelic dysplasia and cleidocranial dysplasia (Table 2).

Newly formed chondrocytes within the immature skeletal architecture subsequently undergo an elaborate process involving proliferation, differentiation, and growth. Throughout these changes, the chondrocytes are supported by a complex array of organic molecules, referred to as the extracellular matrix. This matrix, which includes collagen, proteoglycans, and glycoproteins, not only provides critical structural support but also interacts directly with the signaling pathways modulating chondrocyte development. A disruption of either this complex structural matrix or the intricate molecular signaling pathways regulating chondrocyte growth and development leads to many of the known skeletal dysplasias.

The final step in the formation of bone is mineralization. Osteoblasts deposit an osteoid matrix, which becomes impregnated with hydroxyapatite crystals. This calcified material provides bone with its characteristic

<table>
<thead>
<tr>
<th>Developmental Stage</th>
<th>Timing</th>
<th>Example Pathway/Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patterning</td>
<td>Third through sixth weeks</td>
<td>Notch signaling occurs in oscillations that pattern somite formation. Mutation of the Notch ligand, dll3, leads to autosomal recessive spondylocostal dysostosis, a disorder characterized by multiple abnormalities of the axial skeletal system (hemivertebrae; fused and block vertebrae; and abnormal, fused ribs).</td>
</tr>
<tr>
<td>Condensation and Differentiation</td>
<td>Fifth week onwards</td>
<td>The Sox family of transcription factors (eg, SOX5, SOX6, and SOX9) plays an essential role in the differentiation of precursor cells into chondrocytes in endochondral bone. Campomelic dysplasia is due to haploinsufficiency of SOX9, which leads to bowing and angulation of long bones, hypoplasia of the scapula and pelvis, abnormalities of the ribs and vertebral column, and craniofacial abnormalities. This condition usually is fatal in the neonatal period due to a small rib cage, narrow airways, and hypoplastic lungs. Because of the importance of this gene in sexual differentiation, 75% of 46,XY patients also have complete or partial sex reversal.</td>
</tr>
<tr>
<td>Growth</td>
<td>Fifth week through adolescence</td>
<td>PTHrP is a secreted molecule that maintains chondrocytes in the nonhypertrophic proliferating state. It is signals through the PTH/PTHrP receptor (PTHR) and is regulated indirectly by the Indian hedgehog gene. Abnormalities in this pathway lead to a spectrum of disorders, including Blomstrand chondrodysplasia, Jansen-type metaphyseal chondrodysplasia, and enchondromatosis. For example, homozygous loss-of-function mutations in the receptor for PTHrP lead to excessive chondrocyte hypertrophy and inadequate proliferation. The result is Blomstrand chondrodysplasia, a severe short-limb dwarfism characterized by accelerated bone maturation and generalized sclerosis of bone. It is usually fatal in the neonatal period.</td>
</tr>
<tr>
<td>Mineralization and Homeostasis</td>
<td>Eighth week through adulthood</td>
<td>Mutations in the gene encoding tissue-nonspecific alkaline phosphatase (TnA1P) result in hypophosphatasia. This disorder can manifest in one of six recognized clinical forms: perinatal lethal, perinatal benign, infantile, childhood, adult, and odontohypophosphatasia. Fetuses affected by the perinatal lethal form have markedly impaired bone mineralization in utero, with characteristic osteochondral spurs on the arms and legs. Death usually results at or shortly after birth from respiratory failure due to hypoplastic lungs and rachitic changes of the chest. The infantile form may not be clinically evident at birth but subsequently manifests with similar respiratory complications, craniosynostosis, and symptomatic hypercalcemia.</td>
</tr>
</tbody>
</table>
hard, durable structure. A delicate balance between bone-forming cells (osteoblasts) and bone-degrading cells (osteoclasts) continues throughout life, reshaping and remodeling the skeleton. A variety of skeletal disorders result from the disruption of normal mineralization and homeostasis (Table 2).

**Initial Diagnostic Approach**

The evaluation and initial treatment of the neonate who has a suspected disorder of skeletal development is a multidisciplinary endeavor, requiring, at minimum, the expertise of neonatologists, medical geneticists, and radiologists. After addressing any respiratory compromise and clinically stabilizing the infant, initial evaluation should begin with a detailed history and physical examination. A comprehensive prenatal history should be elicited, looking for potential infectious, environmental, or teratogenic disruptions of skeletal development. A family history also may be informative because many of the disorders of skeletal development are transmitted in an autosomal dominant pattern. Theoretically, affected individuals transmit the trait to 50% of their offspring with this mode of inheritance. In actuality, the numbers are lower due to germline mosaicism and incomplete penetrance. More often, there is no family history of the disorder due to de novo mutations. More than 80% of cases of achondroplasia, for example, are due to de novo mutations in FGFR3, and there is a well-described association between these new mutations and advanced paternal age.

A head-to-toe physical examination should be performed, focusing on physical features and other birth defects that may aid in determining a specific diagnosis (Table 3). The head shape, fontanelles, and suture width are examined, looking for the presence of a craniosynostosis. In addition, any dysmorphic facial features should be noted. The oral cavity is examined for cleft palate, gingival frenulae, and abnormal dentition. Consultation with an ophthalmologist may be indicated to examine for retinitis pigmentosa, cataracts, colobomas, or myopia. Abnormalities of the skin, hair, and nails should be noted and the joints examined carefully for any abnormalities, such as hyperlaxity or contractures. In noting any asymmetry or deformity of the extremities, it is important to look specifically for syndactyly or an abnormal number of digits. Careful cardiac and neurologic examinations should be completed to look for evidence of congenital heart disease or central nervous system (CNS) dysfunction, respectively. Finally, a complete skeletal survey should be performed and consultation with a medical geneticist and pediatric radiologist obtained.

**Radiology**

A skeletal survey performed for the assessment of a potential abnormality of skeletal development should...
include the following views: anteroposterior (AP) and lateral skull; AP and lateral thoracolumbar spine; and AP images of chest, pelvis, upper and lower limbs, and hands/feet. Additional films may be obtained to assess specific abnormalities or if asymmetry exists.

A brief review of all of the radiographs can identify the portion(s) of the skeleton that appear to be affected most severely. Common terms used to refer to regions of the axial skeleton appear in Table 4. Abnormalities of the appendicular skeleton are referred to by the region most affected within individual long bones (epiphyseal, metaphyseal, diaphyseal) as well as along the proximo-distal axis. Shortening that predominantly involves the proximal, middle, or distal region is referred to as rhizomelic, mesomelic, or acromelic, respectively.

In the neonate, epiphyseal dysplasias typically manifest as delayed epiphyseal ossification. The following ossification centers are expected to be seen radiographically in a term or near-term neonate: humeral head, distal femoral, proximal tibial, calcaneus, and talus. Radiographic findings of metaphyseal dysplasias include irregular, broad, and cupped (or lucent) metaphyses. The term “overtubulated” (metaphyseal flaring resulting in a sharp transition between the metaphysis and diaphysis) is used occasionally to describe the radiographic findings of metaphyseal dysplasias. Diaphyseal dysplasias present as relatively wide diaphyses with narrow metaphyses and are often referred to as “undertubulated” bones. Involvement of the spine (most often platyspondyly in the neonate) frequently is seen in conjunction with abnormalities of the long bones. In such cases, the categorization is spondyloepiphyseal, spondylometaphyseal, or spondyloepimetaphyseal dysplasia. This basic information of radiographic and clinical categorization provides the starting point for a query of major reference books and electronic databases.

For examination of individual bones, Offiah and Hall (4) have proposed a helpful mnemonic of “the five S’s”: Structure, Shape, Size, Sum, and Soft tissues. Peculiar or unusual features of individual bones may provide helpful diagnostic clues. It is important to look for increased or decreased bone density, abnormal bony growths, and any bones that appear to be of an unusual shape. The size of individual bones, particularly with respect to the remainder of the skeleton, should be considered. Finally, it is important to note whether there is an abnormal number or fusion of any bones and whether there appears to be any soft-tissue involvement.

### Additional Diagnostic Testing

Depending on the specific disorder of skeletal development, it may be possible to establish a diagnosis with a clinical history, physical examination, and skeletal survey alone. In other cases, additional evaluation may be required. Histologic examination of bone and cartilage may be very informative, although it can be obtained only through bone biopsy. Therefore, it is often reserved for autopsy cases or for infants and children undergoing a surgical procedure for another indication. Biochemical analysis may be helpful in specific cases, such as examination of type I collagen in osteogenesis imperfecta. Finally, DNA testing now is available for many disorders of skeletal development and generally is preferred because it is less invasive and can provide a definitive diagnosis. The utility of these tests varies greatly between disorders, and interpretation of results can be difficult, so consultation with a medical geneticist is advised.

### Prenatal Diagnosis of Fetal Skeletal Dysplasias

Due to improvements in fetal imaging technology, it is now possible to recognize disorders of skeletal development in the prenatal period. Suspicion for a fetal skeletal dysplasia should be raised when routine ultrasonographic measurements of femora or humeri fall below the 5th percentile or other skeletal abnormalities are apparent. Any fetus meeting these criteria should be referred to a high-risk perinatal center that has expertise in fetal skeletal dysplasias for complete ultrasonographic evaluation. Additional imaging studies may include three-dimensional ultrasonography for better definition of craniofacial abnormalities and fetal magnetic resonance imaging if there is a concern for spinal defects. Despite these sophisticated imaging modalities, establishing a definitive diagnosis in the prenatal period remains very difficult. This dilemma presents a major challenge for both obstetricians and neonatologists in

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**Table 4. Terminology: Axial Skeleton**

| Skull: Crania-/cranial  |
| Face: Facio-/facial    |
| Mandible: Mandibulo-  |
| Clavicle: Cleido-      |
| Ribs: Costo-          |
| Spine: Scondylo-/vertebral |
| Pelvis: Ischio-/ilio-/pubic |

Adapted from Offiah and Hal. (4)
<table>
<thead>
<tr>
<th>Nosology Group</th>
<th>Name of Disorder</th>
<th>Key Clinical and Radiographic Features</th>
<th>Inheritance</th>
<th>Loci/Genes</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>FGFR3 group (1)*</td>
<td>Thanatophoric dysplasia</td>
<td>Narrow thorax with respiratory insufficiency, very short extremities and normal trunk length, large head with depressed nasal bridge, “cloverleaf” skull deformity, short and broad long bones (bowed, “telephone receiver” femurs in type 1), central nervous system malformations</td>
<td>Autosomal Dominant</td>
<td>4p16 (FGFR3)</td>
<td>Lethal</td>
</tr>
<tr>
<td></td>
<td>Achondroplasia</td>
<td>Disproportionate shortening of limbs and rhizomelia, with relatively normal trunk length and macrocephaly; “trident” hand; flat vertebrae, round– to square-shaped pelvis, short wide tubular bones; hypotonia in infancy; hydrocephalus; stenosis of foramen magnum; hearing loss; recurrent acute otitis media; normal intelligence</td>
<td>Autosomal Dominant</td>
<td>4p16 (FGFR3)</td>
<td>Excellent</td>
</tr>
<tr>
<td></td>
<td>Hypochondroplasia</td>
<td>Similar to achondroplasia, but milder; onset during second decade of life</td>
<td>Autosomal Dominant</td>
<td>4p16 (FGFR3)</td>
<td>Excellent</td>
</tr>
<tr>
<td>Type II collagen group (2–3)*</td>
<td>Achondrogenesis type II</td>
<td>Hydropic appearance, with short trunk, prominent abdomen, severe micromelia; absent/severely retarded ossification of vertebral bodies and sacrum; small iliac bones; short tubular bones with metaphyseal flare/cupping. Stillborn or death within first hours of birth.</td>
<td>Autosomal Dominant</td>
<td>12q13 (COL2A1)</td>
<td>Very poor</td>
</tr>
<tr>
<td></td>
<td>Hypochondrogenesis</td>
<td>Similar to achondrogenesis type 2, but better ossification of spine, pelvis, and long bones. Most born alive, but die from respiratory failure during first 3 postnatal months.</td>
<td>Autosomal Dominant</td>
<td>12q13 (COL2A1)</td>
<td>Poor</td>
</tr>
<tr>
<td></td>
<td>Kniest dysplasia</td>
<td>Thoracic kyphoscoliosis, marked lumbar lordosis, platyspondyly, anterior vertebral wedging, coronal clefts; flat mid-face, depressed nasal bridge, cleft palate; decreased joint mobility; delayed ossification and deformation of epiphyses. Myopia, retinal detachment, chronic otitis media, hearing loss.</td>
<td>Autosomal Dominant</td>
<td>12q13 (COL2A1)</td>
<td>Fair to good</td>
</tr>
<tr>
<td></td>
<td>Spondyloepiphyseal dysplasia cong.</td>
<td>Similar to Kniest dysplasia but typically milder, normal tubular bones of hands/feet, vertebral coronal clefts typically absent</td>
<td>Autosomal Dominant</td>
<td>12q13 (COL2A1)</td>
<td>Fair to good</td>
</tr>
<tr>
<td></td>
<td>Stickler syndrome (type I)</td>
<td>Midface hypoplasia, small upturned nose, micrognathia; joint hypermobility; vertebral coronal clefts, widened epiphyses; cleft palate, Pierre–Robin sequence, sensorineural hearing loss, myopia, retinal detachment, cataracts</td>
<td>Autosomal Dominant</td>
<td>12q13 (COL2A1)</td>
<td>Good</td>
</tr>
</tbody>
</table>

(continued)
counseling the families of affected fetuses and optimally planning for their postnatal care.

In some cases, prenatal DNA testing may be employed to help establish a definitive fetal diagnosis. For families that have a history of a specific disorder of skeletal development that has been confirmed with molecular methods, mutation analysis may be performed on DNA obtained by chorionic villus sampling or amniocentesis. In the absence of a family history, large gene sizes, "private" mutations, and disorders of unknown cause may hinder timely molecular diagnosis. In many cases, however, it still may be possible to perform successful mutation analysis when a known, common mutation exists (as with FGFR3 mutations in thanatophoric dysplasia and achondroplasia). The interested reader is referred to Krakow and associates (5) for an excellent and more complete discussion of this topic.

Selected Disorders of Skeletal Development With Neonatal Onset

A summary of some of the more common and clinically important disorders of skeletal development presenting in the perinatal and neonatal periods appears in Table 5.

Table 5. A Summary of Neonatally Manifested Skeletal Dysplasias—Continued

<table>
<thead>
<tr>
<th>Nosology Group</th>
<th>Name of Disorder</th>
<th>Key Clinical and Radiographic Features</th>
<th>Inheritance</th>
<th>Loci/Genes</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-rib dysplasia group (7)*</td>
<td>Ellis-van Crevel syndrome</td>
<td>Narrow, shallow thorax; pre- and postaxial polydactyly, fusion of the metacarpals or phalanges, dysplasia of the pelvis, rhizomelia; congenital heart disease; hypoplastic nails; dental anomalies</td>
<td>Autosomal Recessive</td>
<td>4p16 (EVC1, EVC2)</td>
<td>Good in absence of cardiopulmonary abnormalities</td>
</tr>
<tr>
<td></td>
<td>Asphyxiating thoracic dysplasia (Jeune)</td>
<td>Narrow, shallow thorax with respiratory insufficiency; metaphyseal irregularities, short hands/feet, postaxial polydactyly, short middle and distal phalanges, cone-shaped epiphyses; progressive renal disease, pancreatic and hepatic fibrosis, Hirschsprung disease, multiple gingival frenulae, hydrocephalus</td>
<td>Autosomal Recessive</td>
<td>3q24–26 (IFT80), 15q13</td>
<td>Fair</td>
</tr>
<tr>
<td>Decreased bone density group (24)*</td>
<td>Osteogenesis imperfecta</td>
<td>See Table 6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased bone density group (24)*</td>
<td>Osteogenesis imperfecta</td>
<td>See Table 6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Defective mineralization group (25)*</td>
<td>Hypophosphatasia, perinatal lethal</td>
<td>Severe undermineralization of bone; marked shortening of extremities; osteochondral spurs on arms/legs; respiratory failure, apnea, seizures</td>
<td>Autosomal Recessive</td>
<td>1p36 (TNAP)</td>
<td>Poor</td>
</tr>
<tr>
<td>Defective mineralization group (25)*</td>
<td>Hypophosphatasia, infantile forms</td>
<td>May appear normal at birth, but symptoms almost always manifest in first 6 postnatal months. Marked undermineralization of bone on radiography, rachitic changes of metaphyses, craniosynostosis, respiratory insufficiency, symptomatic hypercalcemia, short stature, premature loss of deciduous teeth</td>
<td>Autosomal Recessive</td>
<td>1p36 (TNAP)</td>
<td>Variable</td>
</tr>
</tbody>
</table>

*Numbers in parentheses refer to the group number as they appear in the International Nosology Classification System. (6)
terized by disproportionate involvement of the spine and epiphyses of long bones (spondyloepiphyseal involvement).

Infants who have achondrogenesis type II (Langer-Saldino type) are the most severely affected and typically are stillborn or die within the first few hours of birth. The affected neonate has a hydropic appearance, with very short limbs, flat midface, micrognathia, and a protuberant abdomen. Cleft palate may be present. Radiographically, there is absent or severely delayed ossification of the vertebral bodies and sacrum, short ribs with a barrel-shaped thorax, small iliac bones, and very short tubular bones with metaphyseal flaring and cupping (Fig. 1).

Infants who have hypochondrogenesis have similar features but are less severely affected. The vertebral bodies are more completely ossified (although often still absent in the cervical region), and the tubular bones are not as short. The overall prognosis in this condition is still poor; although most neonates are born alive, many succumb to cardiorespiratory failure during the first few postnatal months.

Although Kniest dysplasia and SEDc usually are recognized at birth, affected infants and children often survive to adulthood and can lead active lives. As with the other type II collagenopathies, there is significant spinal involvement in Kniest dysplasia, with thoracic kyphoscoliosis and marked lumbar lordosis. Radiographs of the spine reveal flattened vertebral bodies (platyspondyly), with anterior wedging and coronal clefts in infancy. There is often a flat midface with depressed nasal bridge and occasionally cleft palate. The extremities are shortened, and joint mobility is decreased. Radiographically, delayed ossification of the capital femoral epiphyses is seen. Once ossified, these epiphyses are broad and flat. The epiphyses of other tubular bones also are deformed. Due to the importance of type II collagen in the structure of the eye and ear, affected children are at risk of myopia, retinal detachment, chronic otitis media, and hearing loss. Patients who have SEDc typically are more mildly affected than those who have Kniest dysplasia. Distinguishing radiologic features of SEDc include absence of vertebral coronal clefts in infancy and normal tubular bones of the hand and feet.

Stickler syndrome may present in infancy with cleft palate and Pierre-Robin sequence. Infants often have midface hypoplasia, a small and upturned nose, micrognathia, and joint hypermobility. Radiographic findings may be evident and most commonly are manifested as vertebral coronal clefts and widened epiphyses of the femora and tibiae. Sensorineural hearing loss, myopia, and later retinal detachment and cataracts may develop.

Disorders Involving Fibroblast Growth Factor-3 (FGFR3)
Mutations in the FGFR3 gene can lead to a variety of skeletal dysplasias that vary greatly in their severity. Thanatophoric dysplasia (TD) and achondroplasia both manifest in the neonatal period, although the former condition is much more severe, typically resulting in death due to respiratory failure in the first few days after birth. Infants affected by TD have very narrow thoraces with consequent pulmonary hypoplasia, very short limbs, and relatively normal trunk lengths (Fig. 2). There is typically a depressed nasal bridge and prominent fore-
head. Craniosynostosis, with a “cloverleaf deformity,” may be present. Skeletal survey reveals short ribs, small and flat vertebral bodies, short and broad pelvic bones, and short and broad tubular bones. There also may be abnormal development of the CNS, including megalencephaly, abnormal temporal lobe development, and disorders of neuronal migration. Rare surviving infants suffer from intellectual disability and seizures. TD has been divided into two subtypes. Type I is characterized by bowed, “telephone receiver” femurs; in type II TD, the femurs are straight and a cloverleaf skull deformity is seen. Each type is caused by distinct mutations in the \( \text{FGFR3} \) gene. Severe achondroplasia with developmental delay and acanthosis nigricans (SADDAN) also is due to \( \text{FGFR3} \) gene mutations. It is very similar to type I TD but has a better prognosis.

Achondroplasia produces changes that are qualitatively similar to TD but invariably less severe. Patients regularly lead active, productive lives well into adulthood. On clinical examination, the limbs appear disproportionately short compared with the remainder of the body. The trunk length appears relatively normal, and the head appears disproportionately large. Moreover, the most proximal segments of the extremities are disproportionately short compared with their more distal counterparts (rhizomelic shortening). A “trident hand” is seen due to short, wide, and “cone-shaped” phalanges. Radiographically, the vertebrae are slightly flat, the pelvis is abnormally shaped (round or slightly square appearance in the neonatal period), and the tubular bones are short and wide (Fig. 3). In early infancy, hypotonia is present, and when combined with a small thorax, can lead to respiratory difficulties and predisposition to recurrent infections. As the affected patient ages, stenosis of the foramen magnum can lead to compression of the brainstem and spinal cord. Untreated, such compression can cause cardiorespiratory compromise and sudden cardiac death. Affected children may suffer from hearing loss, recurrent otitis media, and speech delay. Intellectual development is otherwise normal. Hypochondroplasia is another disorder of skeletal development due to mutations in \( \text{FGFR3} \) and clinically is similar to achondroplasia. However, it is much less severe and usually is not recognized until the end of the first decade of life or later.

**Osteogenesis Imperfecta**

Osteogenesis imperfecta (OI) is a heterogeneous group of disorders characterized by increased bone fragility. As a group, they are the most common disorders of skeletal development that manifest in the neonatal period. OI...
Table 6. Classification and Key Features of Osteogenesis Imperfecta (OI)

<table>
<thead>
<tr>
<th>Type</th>
<th>Notable Clinical and Radiographic Features</th>
<th>Sclera</th>
<th>Dentogenesis Imperfecta</th>
<th>Hearing Loss</th>
<th>Inheritance</th>
<th>Genes/Loci</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>May not be recognized in early infancy, but fractures can occur at birth. Characterized by blue sclerae and normal stature. Fractures typically occur at a rate of a few per year through early childhood and decrease in frequency after puberty. Radiographically, wormian bones, thin cortices, and osteopenia are seen.</td>
<td>Blue</td>
<td>Rare</td>
<td>~50%</td>
<td>Autosomal Dominant</td>
<td>COL1A1 or –2 (quantitative defect)</td>
</tr>
<tr>
<td>II</td>
<td>Evident at birth, most often fatal in first postnatal week. Multiple rib fractures, minimal calvarial mineralization, platyspondyly, marked compression of long bones. Radiographic features: undermineralization, plaques of calcification, severely deformed and crumpled femurs, and small and beaded ribs.</td>
<td>Dark blue</td>
<td>Yes</td>
<td>–</td>
<td>Autosomal Dominant (type IIA)</td>
<td>COL1A1 or –2 (qualitative defect) CRTAP LEPRE1*</td>
</tr>
<tr>
<td>III</td>
<td>Apparent at birth, with multiple fractures in newborn period. Most affected patients survive to adulthood but suffer recurrent fractures, progressive deformity, and extreme short stature. Radiographic features: thin ribs, platyspondyly, thin gracile bones with many fractures, “popcorn” epiphyses, and severe osteoporosis.</td>
<td>Blue</td>
<td>Yes</td>
<td>Frequent</td>
<td>Autosomal Dominant, Autosomal Recessive</td>
<td>COL1A1 or –2 (qualitative defect) CRTAP LEPRE1*</td>
</tr>
<tr>
<td>IV</td>
<td>Characterized by normal-to-grey sclera. Highly variable, ranging from very mild to multiple fractures with progressive deformity. Hearing loss is only seen in some, with onset during adulthood.</td>
<td>Normal to grey</td>
<td>Yes</td>
<td>Occasional</td>
<td>Autosomal Dominant</td>
<td>COL1A1 or –2 (qualitative defect)</td>
</tr>
<tr>
<td>V</td>
<td>Similar to type III/IV (moderate deformity and moderate-to-severe bone fragility), but characterized by hypertrophic callus formation and calcification of the radioulnar interosseous membrane. Histologically, an irregular, meshlike arrangement of lamellae is seen.</td>
<td>Normal</td>
<td>No</td>
<td>No</td>
<td>Autosomal Dominant</td>
<td>Unknown</td>
</tr>
<tr>
<td>VI</td>
<td>Clinically similar to type IV OI but with a somewhat higher fracture rate. Characterized by a distinctive “fish-scale” pattern of lamellae and excessive osteoid on bone histology.</td>
<td>Normal</td>
<td>No</td>
<td>No</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>VII</td>
<td>Characterized by autosomal recessive inheritance; multiple fractures at birth and frequent fractures throughout early childhood; and absence of blue sclerae, dentogenesis imperfecta, and hearing loss. Originally described in First Nations Community in Northern Quebec. Marked rhizomelic shortening seen on radiographs.</td>
<td>Normal</td>
<td>No</td>
<td>No</td>
<td>Autosomal Recessive</td>
<td>CRTAP</td>
</tr>
<tr>
<td>VIII</td>
<td>Similar to type II/III, but distinguished by white sclerae, round face, and a short, barrel-shaped chest. There is also severe growth deficiency, extreme skeletal undermineralization, and bulbous metaphyses. Most described cases were in individuals of African, African American, or Afro-Caribbean descent.</td>
<td>Normal</td>
<td>No</td>
<td>?</td>
<td>Autosomal Recessive</td>
<td>LEPRE1</td>
</tr>
<tr>
<td>IX</td>
<td>Clinically identical to type II/III but with a distinct molecular cause.</td>
<td>Grey</td>
<td>No</td>
<td>?</td>
<td>Autosomal Recessive</td>
<td>PP1B (15q21–22)</td>
</tr>
</tbody>
</table>

*In the prenatal and neonatal period, it is typically impossible to distinguish clinically severe OI caused by defects in type I collagen from severe OI caused by recessive mutations in CRTAP and LEPRE1. However, individuals who have demonstrable mutations in genes causing recessive OI should be designated as type VII, VIII, or IX, rather than type II or III.
initially was divided into four types based on clinical features and mode of inheritance. (7) As the molecular basis for OI has become better established, this classification system has grown to include nine types (Table 6). Type II (perinatal lethal) OI is the most severe form of the disorder, typically leading to death in the perinatal period or early infancy due to respiratory failure. There is diffuse osteoporosis, with multiple fractures and callus formation by the time of birth. The skull is poorly developed, and the ribs and long bones are short and take on a beaded or “wavy” appearance (Fig. 4).

OI types III through IX are characterized by moderate-to-severe bone fragility and often manifest in infancy. In addition to frequent pathologic fractures, common clinical features of OI include short stature, scoliosis, ligamentous laxity, hernias, easy bruising, and hearing loss. Many (but not all) types also are associated with blue sclerae and dentogenesis imperfecta (discolored translucent dentin that is weak and susceptible to excessive wear and damage). Wormian bones (small irregular bones of the skull along suture lines) (Fig. 5) may be seen. Complications include bowing of long bones with progressive deformity, mixed hearing loss, and spinal cord compression due to progressive kyphoscoliosis and vertebral fractures. Type I OI (nondeforming) is the mildest form of the disorder. Although it may be recognized occasionally in the perinatal or neonatal period due to femoral bowing or fractures, fractures typically do not occur until the affected child begins to walk.

In 90% of cases, OI is due to mutations in one of the two genes that encodes for type I collagen (COL1A1, COL1A2). Type I collagen, a major structural element in bones, tendons, ligaments, skin, and sclerae, is formed from three coiled polypeptides. The first step in its synthesis involves chemical modification (hydroxylation of proline and lysine residues), followed by the winding of two alpha-1 helices and one alpha-2 helix together into a single chain to produce procollagen. Both ends of the procollagen subsequently are cleaved to produce the final product, known as tropocollagen. Various insertions, deletions, and point mutations have been described in both genes. Deletions or mutations that lead to truncation of the alpha-helical polypeptide and decreased production of structurally normal collagen generally cause type I OI (the mildest type). Mutations that result in structural changes with qualitatively abnormal collagen cause types II, III, and IV OI. However, it is often difficult to distinguish between these types based on mutation analysis alone.

In 10% of cases of OI, no mutation can be identified in
either *COLIA* gene. Recently, three genes have been described that when mutated, can lead to severe OI transmitted in an autosomal recessive pattern. These genes encode for the proteins cartilage-associated protein (*CRTAP*), leprecan-like 1 (*LEPRE1*) and peptidyl-prolyl isomerase B (*PPIB*), which form an interactive complex. It is not clear whether the underlying mechanism is defective formation of this complex of proteins or defective hydroxylation of the proline 936 residue of type I collagen. Up to 5% of cases of type II OI may be due to mutations in these genes. Type VII OI, characterized by moderate deformation, white sclera, absence of dentogenesis imperfecta, fish-scale pattern of bone lamellation, and an autosomal recessive pattern of inheritance, also has been mapped to the *CRTAP* gene region. Homozygous (recessive) mutations in *PPIB* have been identified in type IX OI. Finally, it has been proposed that patients who have OI due to mutations in *CRTAP* or *LEPRE1* that appear clinically distinct from type II or type VII OI should be classified as type VIII.

Because the dominant and recessive forms of OI are not easily distinguished clinically, DNA testing is necessary to provide accurate diagnostic, management, and recurrence risk information. We recommend starting with sequencing of *COLIA1* and *COLIA2*, and if this is normal, proceeding to sequencing of *CRTAP*, *LEPRE1*, and *PPIB*.
Chondrodysplasia Punctata Group

The chondrodysplasia punctata syndromes are characterized by small calcifications in cartilaginous epiphyses (punctuate epiphyses, stippled epiphyses) (Fig. 6) that are the result of dysynchronous ossification. In addition to inherited osteochondrodysplasias, a wide range of other conditions, including peroxisomal disorders (Zellweger syndrome), chromosomal abnormalities (trisomy 18 and 21, Turner syndrome), single-gene disorders (Cornelia de Lange syndrome), metabolic disorders (GM-1 gangliosidosis, galactosialidosis), infections (congenital rubella), or toxic exposures (maternal diabetes, warfarin embryopathy) can lead to stippled epiphyses. The pattern and location of the stippling often help to establish a specific diagnosis, which is critical to accurate counseling and management. For example, Greenberg dysplasia almost always leads to death in utero or at birth, whereas the tibial-metacarpal type of chondrodysplasia punctata has a very good prognosis, with normal development and survival to adulthood. Interestingly, in all of these conditions, the epiphyseal stippling disappears by about 3 to 5 years of age, making subsequent diagnosis much more difficult.

Asphyxiating Thoracic Dystrophy (Jeune Syndrome)

Asphyxiating thoracic dystrophy is characterized by a very narrow and shallow thorax, which can lead to severe respiratory compromise. Patients have short extremities with metaphyseal irregularities, short hands and feet with postaxial polydactyly, and short middle and distal phalanges with cone-shaped epiphyses. Other associated medical problems include progressive renal disease, pancreatic and hepatic fibrosis, Hirschsprung disease, and hydrocephalus. Respiratory distress and recurrent respiratory infections are the greatest cause of morbidity and mortality during the neonatal period and infancy. The disorder is transmitted in an autosomal recessive pattern, and two genetic loci have been identified to date. A subset of cases are due to mutations in intraflagellar transport protein (IFT80), located in 3q24-q26. Other cases have been mapped to the 15q13 region, but a causal gene has yet to be identified. It can be difficult to distinguish this disorder from Ellis-van Creveld syndrome.

Chondroectodermal Dysplasia (Ellis–van Creveld Syndrome)

Ellis-van Creveld syndrome, originally described in the Amish population, has many similarities with Jeune syndrome. Skeletal changes include narrow thorax (Fig. 7), pre- or postaxial polydactyly, fusion of the metacarpals or phalanges (Fig. 8), dysplasia of the pelvis, and progressive shortening of the extremities in a proximal-to-distal pattern. Multiple gingival frenulae are common. In contrast to Jeune syndrome, however, Ellis-van Creveld syndrome commonly is associated with congenital heart disease, hypoplastic nails (Fig. 8), and dental anomalies (eg, natal teeth, partial odontia, enamel hypoplasia, dysplastic teeth). The most commonly seen cardiac lesions are atrial septal defect or single atrium.

Management

The care of children who have disorders of skeletal development presenting in the neonatal period is a complex, multidisciplinary effort best coordinated by a center with expertise in these conditions. Neonatologists play a crucial role in the stabilization and initial identification of affected infants because many have a variety of medical complications shortly after birth, including respiratory distress due to pulmonary hypoplasia and restrictive lung disease. Medical geneticists and radiologists play critical roles in establishing a definitive diagnosis, which is crucial to provide neonatologists and families with prognos-

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Figure 8. Hands in Ellis-van Creveld syndrome. A. Note the short, broad fingers and deep-set, hypoplastic, ridged fingernails. B. Radiography reveals cone-shaped epiphyses of the phalanges (white arrow), and fusion of the fourth and fifth metacarpals and the capitate and hamate bones.
tic information to direct the overall course and intensity of care. Pediatric orthopedists, physical medicine and rehabilitation specialists, and physical and occupational therapists are needed to monitor the physical development of the children and address specific deformities. Depending on the disorder, a host of specialists may be involved in the affected child’s care, including but not limited to pulmonology (eg, pulmonary hypoplasia, restrictive lung disease), cardiology, dentistry, nephrology, ophthalmology (eg, cataracts, retinal detachment, myopia), otolaryngology, and neurosurgery (eg, stenosis of the foramen magnum, hydrocephalus). Equally important, psychologists, social workers, and family support groups take critical parts in the psychosocial care of patients and their families.

Few pharmacologic treatments are available for the management of disorders of skeletal development. Intravenous infusion of pamidronate (a bisphosphonate) has been reported to increased bone mineral density, decrease biochemical markers of bone reabsorption, and possibly decrease fracture risk in OI. This is presently the standard of care for types III and IV OI. Human growth hormone has been employed on an experimental basis to increase final adult height in several skeletal dysplasias, but its use remains controversial.

**Case Continued: Evaluating a Suspected Skeletal Dysplasia**

After transfer the NICU, the patient is stabilized with nasal continuous positive airway pressure. A skeletal survey is performed (Figs. 9 and 10) and a genetics consultation obtained. The most notable features on review of the skeletal

![Figure 9](image9.png)

**Figure 9.** Clinical case lateral radiographic spine series shows flattened oval to square-shaped vertebrae with irregular ossification throughout, and a single vertebral coronal cleft at L2 (black arrow). The ends of the ribs are broad and cupped.

![Figure 10](image10.png)

**Figure 10.** Clinical case "babygram" shows a narrow rib cage with relatively unremarkable ribs. There is platyspondyly and absence of distal femoral and proximal tibial ossification centers, which normally are present at birth.
survey are vertebral abnormalities and an absence of epiphyses normally present at birth. Vertebrae are flattened oval to square-shaped, with irregular ossification throughout. A single vertebral coronal cleft is apparent at L2 (a feature usually not seen in this particular diagnosis). Distal femoral and proximal tibial epiphysical ossification centers are absent (normally present at birth). The rib cage appears somewhat narrow, but the ribs themselves are grossly normal. Summarizing these preliminary data, the infant appears to be affected by a disorder of skeletal development with prominent spondyloepiphyseal involvement.

This specific pattern of skeletal involvement can be used to search for spondyloepiphyseal dysplasias presenting in the newborn period in “The Nosology and Classification of Genetic Skeletal Disorders”; major atlases, such as Bone Dysplasias and Taybi & Lachman’s Radiology of Syndromes, Metabolic Disorders, and Skeletal Dysplasias; public electronic databases, such as Online Mendelian Inheritance in Man; and commercial databases, such as the London Dysmorphology Database and the Radiological Electronic Atlas of Malformation Syndromes and Skeletal Dysplasia. In this case, consultation with experts in radiology and medical genetics establishes a diagnosis of a type II collagenopathy, most likely spondyloepiphyseal dysplasia congenita, on clinical and radiologic grounds.

Genetic testing is conducted to confirm the diagnosis. A query of www.genetests.org can be performed to identify clinical laboratories offering testing for this and other skeletal dysplasias. In this case, sequence analysis of the entire coding region of COL2A1 is performed, which reveals a 1546G>A missense mutation in exon 22, converting a conserved glycine in the triple helical domain to serine (Gly316Ser). A similar mutation (Gly316Asp) had been reported previously in a patient who had achondrogenesis type II. (8)

The patient has a prolonged NICU stay due to respiratory failure from pulmonary hypoplasia, which requires long-term mechanical ventilation and tracheostomy placement. A gastrostomy tube also is placed due to inability to feed orally. Further evaluation reveals moderate-to-profound hearing loss bilaterally, mild myopia, and cervical spine instability requiring use of a Minerva stabilizing brace. The patient is discharged from the hospital at approximately 9 weeks of age.

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American Board of Pediatrics Neonatal-Perinatal Medicine Content Specification
- Recognize the clinical features and know how to diagnose and manage skeletal dysplasias, such as achondrogenesis, achondroplasia, chondrodysplasia, epiphyseal dysostosis, osteogenesis imperfecta, hypophosphatasia, etc.

References

Suggested Reading
Mornet E. Hypophosphatasia. *Orphanet J Rare Dis.* 2007;2:40
1. Development of the skeleton begins early in embryonic life, starting with patterning of the somites and formation of the limb buds in the third and fourth weeks of embryogenesis. Of the following, abnormalities in early patterning events during skeletal development are most likely to result in:

A. Disruptions.
B. Dysostosis.
C. Osteolysis.
D. Primary dysplasia.
E. Secondary dysplasia.

2. When evaluating a neonate who has a skeletal disorder, it is important to perform a detailed clinical examination, focusing on physical features and other birth defects that may aid in determining a specific diagnosis. Of the following, large fontanelles and wide sutures are most notable for:

A. Campomelic dysplasia.
B. Chondrodysplasia punctata.
C. Cleidocranial dysplasia.
D. Osteogenesis imperfecta.
E. Spondyloepiphyseal dysplasia.

3. For families with a history of a specific disorder of skeletal development that has been confirmed with molecular methods, mutation analysis may be performed on DNA obtained by chorionic villus sampling or amniocentesis. Of the following, the diagnosis of campomelic dysplasia is most likely with a mutation in the gene:

A. COL2A1.
B. FGFR3.
C. IFT80.
D. SOX9.
E. TNAP.

4. You are caring for a 4-day-old female infant whom you suspect has asphyxiating thoracic dystrophy (Jeune syndrome) based on the findings that include a small chest, short hands, and short feet with postaxial polydactyly. The infant is receiving mechanical ventilation, intravenous fluids, and partial enteral feedings. The nurse informs you that the infant has not passed meconium. Of the following, the most likely cause of failure to pass meconium in this infant is:

A. Anal stenosis.
B. Hirschsprung disease.
C. Ileal atresia.
D. Meconium plug.
E. Mid-gut volvulus.

5. You are caring for a term newborn in whom you suspect achondroplasia based on the findings that include rhizomelic shortening of extremities, “trident” hands with “cone-shaped” phalanges, and macrocephaly. You order a radiographic skeletal survey. Of the following, the most specific finding for achondroplasia on imaging of the spine is:

A. Decreasing lumbar interpedicular distance.
B. Hemivertebrae.
C. Spina bifida occulta.
D. Thoracolumbar scoliosis.
E. Vertebral coronal clefts.
Skeletal Dysplasias in the Newborn: Diagnostic Evaluation and Developmental Genetics
Daniel T. Swarr and V. Reid Sutton
NeoReviews 2010;11:e290-e305
DOI: 10.1542/neo.11-6-e290

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